Synthesis of carboxylic acids, esters and their derivatives

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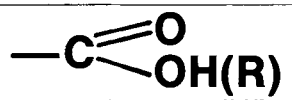

Synthesis of carboxylic acids, esters and their derivatives

by

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and

JAMES F. WOLFE

Virginia Polytechnic Institute and State University

Edited by

SAUL PATAI and ZVI RAPPOPORT

The Hebrew University of Jerusalem

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Foreword

This is the fifth volume in the new series entitled 'Updates from the Chemistry of Functional Groups'.

The volume contains the chapter by Professors M. A. Ogliaruso and J. F. Wolfe entitled 'The synthesis of carboxylic acids and esters and their derivatives' as it appeared in 1979 in '*Supplement B. The chemistry of acid derivatives*'. It is typical of the rapid development of this subject that the 'Appendix' written by the same authors is almost twice as large as the original chapter, although only a decade passed between the preparation of the two.

We will appreciate comments and suggestions regarding the present volume as well as other volumes of the main series or their updates.

Jerusalem
January 1991

SAUL PATAI
ZVI RAPPOPORT

Preface

Carboxylic acids, esters and their derivatives occupy a central position in the chemistry of naturally occurring and synthetic organic compounds. Consequently, methods for the synthesis and interconversions of these functional groups are of prime importance to essentially every practicing organic chemist at one time or another. In view of this, and in order to provide the series, *The Chemistry of Functional Groups*, with a single source of information on general methods for the synthesis of carboxylic acids, esters, acid anhydrides, acyl halides, amides and imides, we authored a chapter on the synthesis of carboxylic acids and their derivatives, which appeared in *Supplement B: The chemistry of acid derivatives, Part 1*, pp. 267–490. That chapter contained descriptions of the most common methods for the synthesis of acids and acid derivatives, with emphasis on preparative techniques that appeared in the primary literature during the period, 1967 through early 1976.

The present monograph volume on the synthesis of carboxylic acids and acid derivatives represents our response to an invitation by the Editors and publishers of the 'Functional Groups' series of books to combine the material contained in the original chapter with new methodology from the literature for the period, 1976 through 1987. The format for this combination consists of the original text as published in 1979, along with an up-to-date Appendix containing the newer material in the same format as used earlier.

This monograph is designed for the practicing chemist who seeks a convenient, single source for synthetic methods leading to carboxylic acids and their derivatives. We have attempted to include sufficient detail and examples of typical preparation to allow the reader to make a rational choice from among several alternative methods. We realize that there are certain to be synthetic procedures that we have failed to include, or have given only cursory attention. For this, we apologize, with the sincere hope that what has been included will be of help and interest to our colleagues in the international organic chemistry community.

We wish to express our gratitude to the Department of Chemistry at Virginia Polytechnic Institute, which has been our professional home for a combined time of nearly half-a-century. To the National Science Foundation, the National Institutes of Health, and the Defense Advanced Research Project Administration, we extend our sincere appreciation for financial support of our research efforts while this monograph was being written. Finally, we thank Marion Bradley Via, without whose generosity this project would have been impossible.

Blacksburg,
Virginia
1991

MICHAEL A. OGLIARUSO
JAMES F. WOLFE

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Edited by Saul Patai and Zvi Rappoport

CHAPTER 1

The synthesis of carboxylic acids and esters and their derivatives

I. INTRODUCTION

Since other volumes in the series, *The Chemistry of Functional Groups*, do not presently contain chapters devoted exclusively to discussions of standard methods for the preparation of carboxylic acids and esters, our major goal in writing this chapter has been to systematically present the most widely applicable procedures for synthesizing these two classes of compounds. We have also included discussions of recent developments in the synthesis of anhydrides, acyl halides, amides and imides.

The primary literature surveyed for this chapter covers mainly the years 1967 through 1975, with some citations from the 1976 literature. Synthetic methods which have been reviewed elsewhere are given brief treatment, and the reader is provided with references to these sources.

We have attempted to include as representative examples of synthetic methods, procedures which are well tested and clearly described. Almost certainly some methods will be overlooked or judged to be of insufficient generality to warrant inclusion. We hope, however, that such instances will be few and that this chapter may be useful to the international community of synthetic organic chemists.

II. SYNTHESIS OF CARBOXYLIC ACIDS

Standard methods for the synthesis of carboxylic acids have been reviewed in the texts by Buehler and Pearson[1] and by Sandler and Karo[2]. More specific reviews published since 1950 have dealt with the synthesis of fatty acids[3-8], dicarboxylic acids[9-12] and polycarboxylic acids[13,14].

A. Acids by Hydrolysis Reactions

Numerous synthetic procedures initially afford carboxylic acid derivatives, which can subsequently be hydrolysed, or cleaved in a fashion analogous to hydrolysis, to give free acids. Esters and nitriles resulting from active-hydrogen condensations and nucleophilic substitutions are encountered most frequently in this context. In addition to the usual acid derivatives, certain other functional groups such as di- and trihalomethyl can be converted into acids by hydrolytic methods.

1. Hydrolysis of esters

Hydrolysis of esters can be carried out in the presence of various acidic or basic reagents. Acidic hydrolysis (equation 1) is a catalytic process in which the products and reactants reach equilibrium concentrations unless the reaction is forced toward

$$R^1COOR^2 + H_2O \overset{H^+}{\rightleftharpoons} R^1COOH + R^2OH \quad (1)$$

the desired acid. In most instances of synthetically useful acidic hydrolyses, water is provided in sufficient excess to favour production of the carboxylic acid and alcohol. Alkaline cleavage of esters (equation 2) is not a catalytic process, since a molar equivalent of hydroxide ion is consumed for each equivalent of ester converted to carboxylate salt.

$$R^1COOR^2 + OH^- \longrightarrow R^1COO^- + R^2OH \quad (2)$$

Because of its essential irreversibility, saponification by aqueous or alcoholic alkali metal hydroxides is the most widely used method for the hydrolytic cleavage of unhindered esters which are not otherwise sensitive to hydroxide ion. Numerous well-tested examples of saponification reactions may be found in the collected volumes of *Organic Syntheses*[15]. Typical of such a process is the hydrolysis of *trans*-methyl 2-methyl-2-dodecenoate to *trans*-2-methyl dodecenoic acid (equation 3)[16] and the saponification of dimethyl hendecanoate to methyl hydrogen

$$C_9H_{19}CH{=}CMeCOOMe \xrightarrow[\text{aq. EtOH}]{KOH} C_6H_{19}CH{=}CMeCOOH \quad (3)$$

hendecanedioate (equation 4)[17]. The latter procedure affords the monoester

$$MeOOC(CH_2)_9COOMe \xrightarrow[MeOH]{Ba(OH)_2} MeOOC(CH_2)_9COOH \quad (4)$$

because the barium salt of this product precipitates from the reaction solution. The hydrolysis of low molecular weight esters by aqueous sodium hydroxide is aided by addition of catalytic amounts of quaternary ammonium salts as phase-transfer catalysts[18].

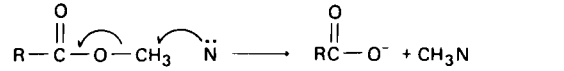
Acidic hydrolysis of esters is often accomplished by refluxing the ester with aqueous hydrochloric acid, alone[19] or in the presence of a suitable cosolvent such as dioxane[20]. Acid-catalysed cleavage becomes the method of choice for esters which contain another functionality which is sensitive to aqueous alkali. For example, methyl 2,3-dibromopropionate is smoothly converted into 2,3-dibromopropionic acid by aqueous hydrobromic acid[21]. However, in some instances it is desirable to effect concomitant saponification and elimination of

base-sensitive groups, e.g. in the preparation of stearolic acid from methyl 9,10-dibromostearate[22] and in the synthesis of muconic acid from α,δ-dibromoadipate[23].

Two major problems arise in the synthesis of carboxylic acids from esters. These are: (*i*) the reluctance of certain esters to undergo either acidic or basic hydrolysis because of steric hindrance, and (*ii*) the sensitivity of various functionally substituted esters to both aqueous acid and base.

Hydrolytic cleavage of sterically hindered esters can be accomplished in several ways. For example, mesitoic esters are hydrolysed by dissolution in 100% sulphuric acid followed by quenching in cold water[24]. More recently, it has been reported that alkyl mesitoates can be saponified in excellent yields by the potassium hydroxide complex of the macrocyclic ether, dicyclohexyl-18-crown-6 in refluxing benzene or toluene[25].

A useful approach to the cleavage of hindered esters involves displacement of carboxylate ion from the alkyl group of the ester by a suitable nucleophilic reagent (equation 5). As would be expected for a bimolecular nucleophilic displacement,



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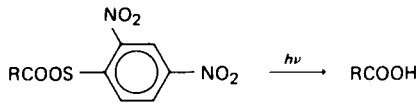
methyl esters participate most readily in such reactions. Lithium iodide in pyridine, 2,6-lutidine or 2,4,6-collidine[26] and potassium *t*-butoxide in dimethyl sulphoxide (DMSO)[27] appear to be the first reagents recognized for their generality in such reactions. Later modifications of these procedures include the use of lithium iodide in dimethylformamide (DMF)[28,29], lithium iodide–sodium cyanide in DMF[30] and dimsyl sodium in DMSO[31,32]. Lithium *n*-propyl mercaptide in hexamethylphosphoramide (HMPA)[33], and sodium ethylmercaptide in DMF[34] readily cleave hindered esters such as methyl triisopropylacetate and methyl *O*-methylpodarpate. Other sulphur nucleophiles such as trithiocarbonate[35] and sodium ethanedithioate[36] in acetonitrile have been used to effect the cleavage of 2-haloethyl esters. The utility of these reagents with hindered esters has not yet been established. 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) has been found to act as an effective non-ionic nucleophile for the cleavage of hindered esters[37]. This reagent has also been used to cleave toluene-*p*-sulphonylethyl esters, presumably by β-elimination of carboxylate ion[38]. Boron trichloride in methylene chloride is an effective reagent for converting hindered esters to acids, although its mechanism of action is obviously not analogous to that of nucleophilic reagents[39].

The problems associated with the synthesis of carboxylic acids from esters containing other hydrolytically unstable functions may be circumvented by employing esters with *O*-alkyl groups which are susceptible to cleavage under anhydrous conditions. Many of the procedures discussed above for hindered esters are satisfactory, provided methyl esters are employed. Classical methods for anhydrous decomposition of esters to acids involves the use of *t*-butyl esters, which can be cleaved thermally[40] or in the presence of anhydrous acid[41,42]. Tetrahydropyranyl esters are likewise sensitive to anhydrous acid[43-46]. Benzyl esters undergo hydrogenolysis to form toluene and carboxylic acids[47-49]. Phenacyl esters can also be cleaved by catalytic hydrogenolysis[50] and by sodium thiophenoxide in anhydrous DMF[50]. Benzyl esters afford acids on treatment with trifluoroacetic acid[51] or formic acid[49].

Photolysis of 2,4-dinitrobenzenesulphenyl esters provides a route to carboxylic acids under mild, anhydrous conditions[52] (equation 6). 2,2′-Dinitrodiphenylmethyl



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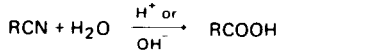
and *o*-nitrobenzyl esters react similarly upon near ultraviolet irradiation to afford carboxylic acids in excellent yields[53].

Lactones can be hydrolysed to afford hydroxy[54] and halo acids[55] using reaction conditions similar to those employed for acyclic ester hydrolysis.

2. *Hydrolysis of nitriles*

The ease with which a cyano group can be introduced into various molecules by nucleophilic displacement, addition to carbonyl groups of aldehydes and ketones, hydrocyanation of α,β-unsaturated carbonyl compounds, and even direct aromatic substitution, makes the nitrile function an extremely useful precursor to carboxylic acids.

Hydrolyses of nitriles can be carried out under basic or acidic conditions (equation 7). The former appear to be employed more frequently than the latter.



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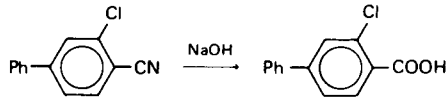
Alkaline hydrolyses are promoted by ethylene glycol[56], diethylene glycol[57] and glycerol[58]. Typical examples of base-promoted hydrolyses of nitriles appear in the syntheses of 3-chlorobiphenyl-4-carboxylic acid[59] (equation 8) and 3-*t*-butylpentanedioic acid[60] (equation 9). The syntheses of cyclopropane carboxylic acid[61] from γ-chlorobutyronitrile and methylsuccinic acid[62] from ethyl crotonate are illustrative of reactions which employ alkaline hydrolysis of a nitrile preceeded by ring closure and hydrocyanation, respectively.



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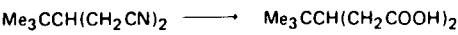

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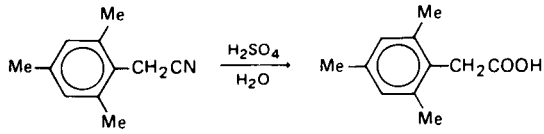
Acidic hydrolyses are typified by the synthesis of mesitylacetic acid from mesitylacetonitrile[63] (equation 10) and by the preparation of *o*-toluic acid from *o*-toluonitrile[64]. Aqueous hydrochloric[65,66] and hydriodic[67] acids are useful reagents for nitrile hydrolysis.



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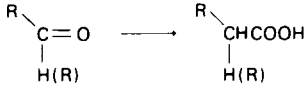
Sterically hindered nitriles can usually be hydrolysed efficiently by alkali hydroxides in ethylene glycol[56] or diethylene glycol[57]. However, in some instances it may be advantageous to first convert the nitrile to a primary amide by means of a suitable reagent such as concentrated sulphuric acid[68] or polyphosphoric acids[69]

and then hydrolyse the amide with nitrous acid. The combined action of sulphuric acid and sodium nitrite on nitriles may be satisfactory without necessitating the isolation of the intermediate amide[70].

Hydrolysis of the nitrile function plays an important role in the synthesis of α-amino acids (Strecker Synthesis)[71-73] and α-hydroxy acids[73,74] from aldehyde and ketone cyanohydrins (equation 11). Cyanohydrin formation and hydrolysis can also serve as a method for homologation of aldehyde and ketone carbonyl groups to the next higher carboxylic acid[75,76]. A convenient application of this method involves reaction of aromatic aldehydes with glyoxal bisulphite and alkaline cyanide to afford arylacetic acids[77].



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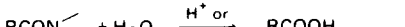
3. *Hydrolysis of amides*

Primary, secondary and tertiary amides, as well as lactams and imides undergo hydrolysis in the presence of alkali hydroxides or mineral acids in much the same manner as do esters and nitriles. Recently, aqueous sodium peroxide has been used



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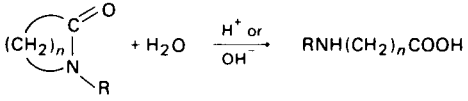

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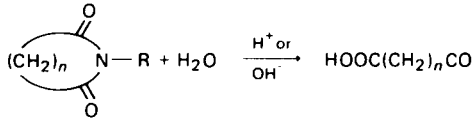
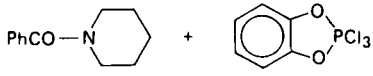


(14)

to effect the hydrolysis of amides[78]. Certain amides are also converted to acids by *o*-phenylenedioxyphosphorus trichloride[79] (equation 15).

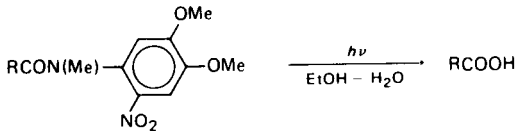


(15)

Hindered amides can be converted to acids by potassium hydroxide in diethylene glycol[80]. Other methods involve the use of nitrous acid[81], or sulphuric acid and sodium nitrite[82], or *n*-butyl nitrite and a mixture of hydrochloric and acetic acids[83]. Hindered secondary amides can be hydrolysed by first converting them into *N*-nitroso derivatives, which then undergo decomposition to afford the acid[84,85]. Nitrosonium fluoroborate[86] in acetonitrile represents an attractive reagent for the hydrolysis of hindered amides under anhydrous conditions.

N-Methyl-*N*-(2-nitro-4,5-dimethoxyphenyl)amides have been found to undergo photolytic cleavage to the respective acids in good yields (equation 16)[87].

Two types of reactions which are analogous to the hydrolysis of amides involve oxidative cleavage of acylhydrazides and hydroxamic acid derivatives. Acylhy-



(16)

drazides afford acids upon treatment with ferric chloride[88], NBS[89], manganese dioxide[90], ceric ammonium nitrate[91], lead tetraacetate[92], sodium hypochlorite[93] and molecular oxygen in the presence of cupric acetate (equation 17)[94]. Hydroxamic acids are cleaved to give carboxylic acids by aqueous periodate (equation 18)[95,96].

$$R^1CONHNHR^2 \xrightarrow{[O]} R^1COOH \tag{17}$$

$$RCH_2CONHOH \xrightarrow{HIO_4} RCOOH \tag{18}$$

4. *Hydrolysis of acyl halides and anhydrides*

Acyl halides and anhydrides can be hydrolysed without the necessity of acidic or basic catalysts (equation 19)[97,98]; however, mineral acids[99], alkali hydroxides[100] and tertiary amines[101] are sometimes used to accelerate the hydrolyses of anhydrides. In general, acyl halides are prepared from the free acid in order to activate the acyl function toward nucleophilic acyl substitution and are therefore seldom employed in hydrolytic preparations of acids.

$$\begin{matrix} RCOCl \\ \text{or} \\ (RCO)_2O \end{matrix} \xrightarrow{H_2O} RCOOH \tag{19}$$

5. *Hydrolysis of trihalides*

A trihalomethyl group serves as a convenient predecessor to the carboxyl function (equation 20). Although the hydrolysis of benzotrichlorides is a

$$RCX_3 + H_2O \xrightarrow[OH^-]{H^+ \text{ or}} RCOOH \tag{20}$$

well-known route to aromatic carboxylic acids, the trihalomethyl group is not so easily introduced into aliphatic molecules as in the aromatic series, where benzylic halogenation of methylated aromatics is readily accomplished. However, telomerization of olefins with carbon tetrachloride affords α,α,α-trichloro-ω-chloroalkanes[102], which then undergo acidic hydrolysis to form ω-chloroacids (equation 21). A frequently encountered method for introduction of a trichloro-

$$Cl(CH_2CH_2)_nCCl_3 \xrightarrow[H_2SO_4]{H_2O} Cl(CH_2CH_2)_nCOOH \tag{21}$$

methyl group into an aliphatic framework involves base-catalysed condensation of aromatic aldehydes with chloroform to afford aryltrichloromethylcarbinols, which can then be hydrolysed by alcoholic potassium hydroxide to give α-alkoxyaryl-

$$ArCH(OH)CCl_3 + KOH \xrightarrow{ROH} ArCH(OR)COOH \quad (22)$$

acetic acids (equation 22)[103-105]. When the condensation and hydrolysis steps are conducted in the presence of aqueous potassium hydroxide[106,107] or under conditions of phase-transfer catalysis[108] α-hydroxy acids are obtained. An interesting synthesis of bicyclo[3.3.0]octane-1-carboxylic acid involves the formation and acid-catalysed hydrolysis of 1-trichloromethylbicyclo[3.3.0]octane[109].

6. *Hydrolysis of dihalides*

Reaction of compounds containing a 1,1-dichlorovinyl group with concentrated sulphuric acid followed by a water quench produces carboxylic acids, often in excellent yields (equation 23)[110]. A reaction sequence which is somewhat related

$$-CH=C\begin{matrix}Cl\\Cl\end{matrix} \xrightarrow[H_2O]{H_2SO_4} -CH_2COOH \quad (23)$$

to the above process, but considerably milder, involves reaction of appropriate carbonium ion precursors, such as secondary or tertiary alcohols, esters of tertiary alcohols or olefins, with 1,1-dichloroethylene (vinylidene chloride) in the presence of concentrated sulphuric acid or sulphuric acid and boron trifluoride. Hydrolysis of the reaction mixture affords the carboxylic acid with two more carbons than the intermediate carbonium ion. The general features of this type of reaction are shown in equation (24). A comprehensive review of the reaction is available[111]. A recent report describes its intramolecular application[112].

$$R^2-\overset{R^1}{\underset{R^3}{C^+}} + CH_2=CCl_2 \longrightarrow R^2-\overset{R^1}{\underset{R^3}{C}}-CH_2\overset{+}{C}Cl_2 \xrightarrow{H_2O} R^2-\overset{R^1}{\underset{R^3}{C}}-CH_2COOH \quad (24)$$

B. Acids by Condensation Reactions

The syntheses described in this section involve active-hydrogen reactions in which carbanions are key intermediates.

1. *Perkin reaction*

This reaction involves condensation of an aryl aldehyde with acetic anhydride or an α-alkylacetic anhydride in the presence of a base such as the carboxylate salt corresponding to the anhydride or a tertiary amine (equation 25). Although the

$$ArCHO + (RCH_2CO)_2O \xrightarrow[\text{or } R_3N]{RCH_2COONa} ArCH=CRCOOH \quad (25)$$

Perkin reaction is probably the most widely used method for the synthesis of cinnamic acids, aliphatic aldehydes containing α-hydrogens do not react satisfactorily. For a more detailed discussion of the scope and limitations of this reaction, the reader is referred to a somewhat dated review[113] and an excellent discussion of the mechanism[114].

2. *Doebner reaction*

Malonic acids serve as the active-hydrogen components in this reaction, which is a modification of the Knoevenagel reaction (see Section III.B.1) using pyridine as the reaction solvent (equation 26). The rather mild conditions associated with the

$$RCHO + CH_2(COOH)_2 \xrightarrow{\text{pyridine}} RCH{=}CHCOOH + CO_2 \quad (26)$$

Doebner reaction permit the use of aliphatic aldehydes, which polymerize rapidly under the more stringent conditions of the Perkin reaction. Thus, this reaction represents a fairly general method for the synthesis of both β-aryl- and β-alkyl α,β-unsaturated acids. Several reviews of the Doebner reaction have been published[114-116].

3. *Stobbe condensation*

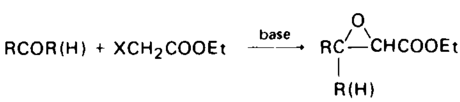
The scope, limitations, and mechanism of this reaction have been reviewed[114,117,118]. The Stobbe reaction involves base-catalysed condensation of diethyl succinate with ketones or aldehydes to form the monoethyl esters of α-alkylidene- or α-aralkylidenesuccinic acids (equation 27). The most satisfactory

$$RCOR(H) + \begin{matrix} CH_2COOC_2H_5 \\ | \\ CH_2COOC_2H_5 \end{matrix} \xrightarrow{\text{base}} \begin{matrix} RC{=}C \\ | \\ R(H) \end{matrix}\begin{matrix} COOC_2H_5 \\ CH_2COOH \end{matrix} \quad (27)$$

bases for this reaction appear to be potassium *t*-butoxide[119] or sodium hydride[118]. The initially formed alkylidene or aralkylidine ethyl hydrogen succinates can be converted into other acid derivatives such as β,γ-unsaturated acids, γ-butyrolactones and γ-keto acids[114,118,120].

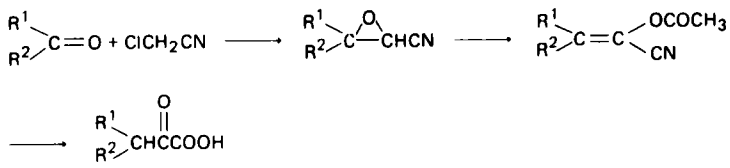
4. *Darzens condensation*

In its most general form, the Darzens reaction[121,122] involves base-catalysed condensation of α-halo esters with ketones or aromatic aldehydes in the presence of strong bases such as alkali metal alcoholates or amides (equation 28). The resulting



α,β-epoxy esters (glycidic esters) can be hydrolysed to glycidic acids, which undergo facile decarboxylation to form aldehydes or ketones, depending upon the nature of the α-halo ester employed as the active-hydrogen component. Although the Darzens condensation is not a widely used method for acid synthesis, the aldehydic product resulting from the decarboxylation step can be oxidized to a carboxylic acid as shown in equation (29)[123]. In a recently reported sequence of reactions (equation 30) similar to the classical Darzens condensation, chloroacetonitrile has been condensed with ketones to afford α,β-epoxynitriles, which undergo ring-opening

$$\begin{matrix} R \\ R(H) \end{matrix}\!\!>C{=}O \xrightarrow[\text{2. oxidation}]{\text{1. Darzens}} \begin{matrix} R \\ R(H) \end{matrix}\!\!>CHCOOH \quad (29)$$



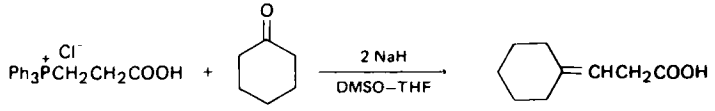
(30)

and elimination upon treatment with hydrogen chloride, acetic anhydride and finally triethylamine, to afford α-cyano vinyl acetates. Acidic or basic hydrolysis of these compounds produces α-keto acids[124].

5. *Wittig-type reactions*

Applications of Wittig-type reactions to the synthesis of free carboxylic acids are encountered much less frequently than those in which esters are the final products. In view of this, the reactions discussed in this section are limited to those in which carboxylic acids are produced directly. Additional examples of the use of Wittig-type reactions for the preparation of esters are discussed in Section III.B.3. A comprehensive review of the Wittig reaction in the synthesis of unsaturated acids and esters has appeared in another volume of this series published in 1969[125]. A recent review of organic phosphonate carbanions as synthetic intermediates includes numerous examples of ester preparations[126].

The most general approach to Wittig-type syntheses of unsaturated acids involves the use of alkylidene phosphoranes containing a free carboxyl group. This procedure is illustrated by the preparation of β-cyclohexylidenepropionic acid (equation 31)[127]. Similar reactions employing other carboxyalkylidenephosphoranes have been used to prepare a variety of unsaturated acids (equation 32)[128–130].



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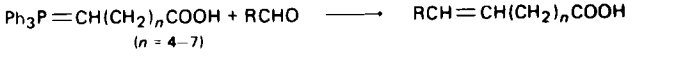
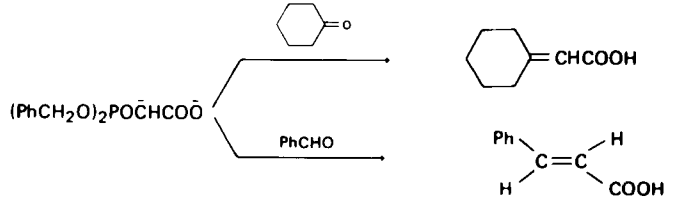


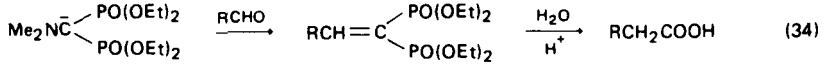
(32)

Carboxyalkyl phosphonates can also be used in the direct synthesis of free carboxylic acids. Thus, the dianion prepared from α-dibenzylphosphonoacetic acid has been employed in the synthesis of several α,β-unsaturated acids (equation 33)[131]. On the basis of these preliminary experiments it would appear that dianions derived from other carboxyalkyl phosphonates could serve as useful intermediates for the synthesis of a variety of unsaturated acids.



(33)

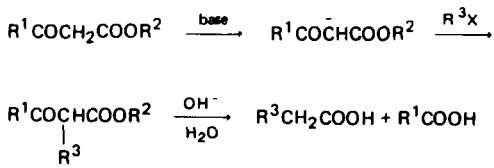
In a novel application of a Wittig-type reaction to the synthesis of carboxylic acids, the carbanion derived from tetraethyl dimethylaminoethylenediphosphonate has been allowed to react with aldehydes to form diethyl 1-dimethylaminoalkenylphosphonates, which can be hydrolysed to α-substituted acetic acids (equation 34)[132].



(34)

6. *Acetoacetic ester synthesis*

The synthesis of carboxylic acids from acetoacetic ester and other β-keto esters involves formation and alkylation of the β-keto ester carbanion, followed by hydrolytic cleavage of the acyl and ester functions of the resulting alkylated β-keto ester (equation 35)[133]. The competing formation of ketonic products resulting

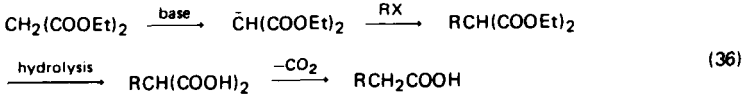


(35)

from decarboxylation of β-keto acids and the presence of two acidic components in the final reaction mixture places this synthesis among the least desirable of active-hydrogen condensations leading to carboxylic acids. However, under certain conditions, the acyl group of α-alkylated β-keto esters can be cleaved without accompanying ester hydrolysis to form α-alkyl acetates, which are isolated and hydrolysed to give α-alkylacetic acids. Such procedures are discussed in Section III.B.5.

7. *Malonic ester synthesis*

This classical method of acid synthesis involves formation and alkylation of the carbanion of malonic esters, followed by hydrolysis and decarboxylation (equation 36). The versatility of the malonic ester synthesis has been demonstrated by its



(36)

application to the preparation of α-substituted acetic acids[134,135], α,α-disubstituted acetic acids[135], dicarboxylic acids[136], cycloalkane carboxylic acids[137], γ-keto acids[138], α-halo acids[139] and α-amino acids[139–144]. Several excellent discussions of the synthetic utility of malonic esters are available[145,146]. Recently[147], diethyl malonate has been shown to undergo alkylation with Δ^1-olefins in the presence of manganese(III) or cobalt(III) acetates to afford 2-alkenylmalonates, which can be hydrolysed to γ,δ-unsaturated acids or cyclized to γ-lactones.

8. *From dianions (α-anions) of carboxylic acids*

A simple, yet elegant alternative to the malonic ester synthesis involves treatment of a carboxylic acid with two molecular equivalents of strong base to produce a dianion intermediate resulting from abstraction of both the carboxyl proton and an α-hydrogen. These dianions react regiospecifically at the α-anion site with electrophilic reagents to form elaborated analogues of the parent acid without requiring ester hydrolysis and decarboxylation.

The α-anion approach was first successfully utilized with phenylacetic acid, which was converted to the dianion by means of potassium or sodium amide in liquid ammonia (equation 37)[148-150]. Alkylations afforded α-substituted phenyl-

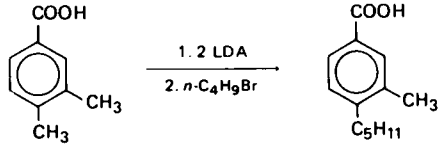
$$PhCH_2COOH \xrightarrow[\text{liq. } NH_3]{2\,KNH_2} PhC\bar{H}COO \xrightarrow{RX} PhCHRCOOH \qquad (37)$$

acetic acids in good yields. Similarly, Ivanov-type[151,152] reagents of arylacetic acids can be prepared by reaction of the acid or acid salt with an alkyl Grignard reagent such as isopropylmagnesium bromide[153]. Subsequent reaction of such reagents with alkyl halides provides the appropriate α-substituted acid (equation 38).

$$PhCHMgBrCOOMgBr \xrightarrow[HMPA]{RX} PhCHRCOOH \qquad (38)$$

The dianion approach to acid synthesis has now been extended significantly by the discovery that aliphatic acids can be converted to dianions by two molecular equivalents of lithium diisopropylamide (LDA) in THF–hexane[154,155]. Alkylations of the resulting dilithio salts can be effected smoothly with alkyl halides that are not prone to undergo β-elimination (equation 39). Toluic and dimethylbenzoic acids also afford dianions, which undergo alkylation as shown in equation (40) for

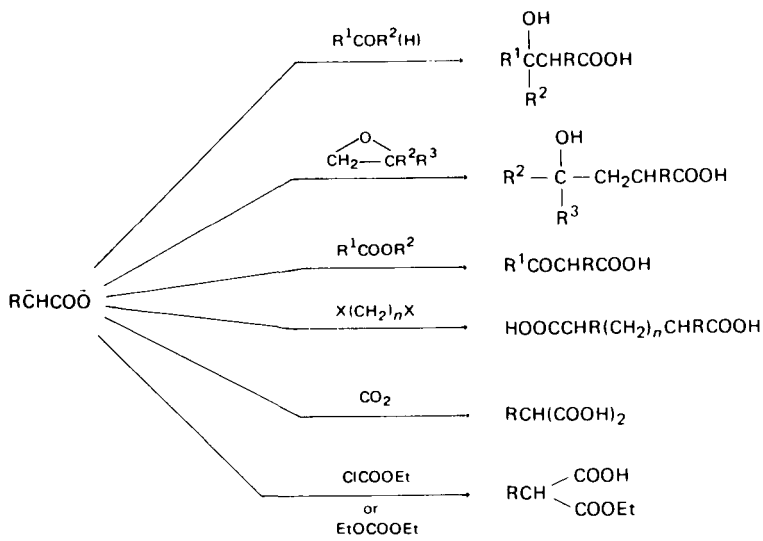
$$R^1R^2CHCOOH \xrightarrow{LDA} R^1R^2\bar{C}COO \xrightarrow{R^3X} R^1R^2R^3CCOOH \qquad (39)$$



(40)

3,4-dimethylbenzoic acid[156]. α-Anion formation can also be accomplished by initial reaction of the acid with sodium hydride in the presence of diisopropylamine, followed by addition of *n*-butyllithium[157,158].

The most generally satisfactory method for formation and alkylation of aliphatic acid dianions appears to involve the use of LDA or a combination of sodium hydride and LDA in THF–hexane[159] or THF–hexane–HMPA[159,160]. In addition to LDA, several other basic reagents can be used for dianion formation. These include lithiumnaphthalene[161-166], sodiumnaphthalene[165-170], sodiumphenanthrene[167] and lithium *t*-butyl amide[171]. Alkali amides[172] and saline hydrides[173] are not sufficiently basic to produce dianions from aliphatic acids under the mild conditions employed with LDA.



(41)

Carboxylic acid dianions serve as convenient intermediates for the synthesis of numerous types of functionalized acids (equation 41). For example, α-anions react with aldehydes and ketones to afford β-hydroxy acids[161,164,169-171,174-176], with certain epoxides to give γ-hydroxy acids and lactones[154,159] with esters to produce β-keto acids[164,178], and with dihalides ($n = 2$–4) to form dicarboxylic acids[154,179,180]. Carboxylation produces malonic acids[166,181], while reaction with ethyl chloroformate or carbonate esters affords alkyl hydrogen malonates[182].

Oxidation of acid dianions with molecular oxygen can afford α-hydroxy or α-hydroperoxy acids[183-185], depending on reaction conditions (equation 42).

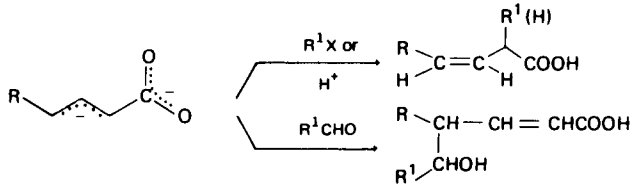
$$R^1R^2\bar{C}COO \xrightarrow{O_2} R^1R^2C(OH)COOH + R^1R^2C(OOH)COOH \quad (42)$$

$$RCH_2\bar{C}HCOO \xrightarrow{DDQ} \begin{matrix} R & & H \\ & C=C & \\ H & & COOH \end{matrix} \quad (43)$$

When 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) is used as an oxidizing agent, (*E*)-α,β-unsaturated acids are obtained in moderate yields (equation 43)[186]. Oxidative dimerization of Ivanov intermediates as well as dialkali salts of carboxylic acids can be effected with ferric chloride[187] and molecular oxygen in the presence of copper(II) salts (equation 44)[188].

$$RCHCOO \xrightarrow[\text{or } O_2, Cu^{2+}]{FeCl_3} \begin{matrix} RCHCOOH \\ | \\ RCHCOOH \end{matrix} \quad (44)$$

Unsaturated acids containing α,β or β,γ double bonds can be converted to delocalized dianions, which undergo protonation and alkylation exclusively at the α-carbon (equation 45)[189,190]. Aldol condensations occur predominantly at the γ-position of such dianions[161,162,191].

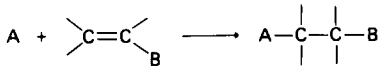


(45)

9. *Michael reactions and related conjugate additions*

Conjugate addition (Michael-type) reactions have been used to excellent advantage in the synthesis of carboxylic acids. A general review of the Michael reaction, published in 1959, includes numerous examples of this reaction in acid and ester preparations[192].

Application of Michael-type reactions to carboxylic acid synthesis takes several general forms based on the interaction of a nucleophilic addend (A) with a conjugated acceptor containing a carbanion stabilizing group (B). In certain cases



both A and B are functions which can be hydrolysed to a carboxy or carboxyalkyl group. In other instances either A or B, but not both, furnishes the carboxy or carboxyalkyl group upon hydrolysis. Hydrocyanation of diethyl benzalmalonate followed by hydrolysis to form phenylsuccinic acid (equation 46)[193] is representative of the first of these approaches. The synthesis of 3-methylheptanoic acid[194] by conjugate addition of *n*-butylmagnesium bromide to *s*-butyl crotonate illustrates the second general approach (equation 47), and also emphasizes the rather widely applicable conjugate addition of Grignard reagents to α,β-unsaturated carbonyl systems. Alkylidene malonic esters[195] and α-bromocrotonic acid[196] have been used as acceptors with Grignard reagents in similar applications of conjugate addition reactions to acid synthesis.

$$PhCH{=}C(COOEt)_2 \xrightarrow[H_2O]{KCN} PhCH(CN)CH_2COOEt \xrightarrow[H_2O]{HCl} PhCH(COOH)CH_2COOH \quad (46)$$

$$CH_3CH{=}CHCOOCHC_2H_5 \xrightarrow[2.\ hydrolysis]{1.\ n\text{-}BuMgBr} n\text{-}BuCHCH_2COOH \quad (47)$$

Conjugate addition of hydroxyl amines[197] as well as primary and secondary amines[198] to α, -unsaturated acids and esters provides a convenient route to β-amino acids.

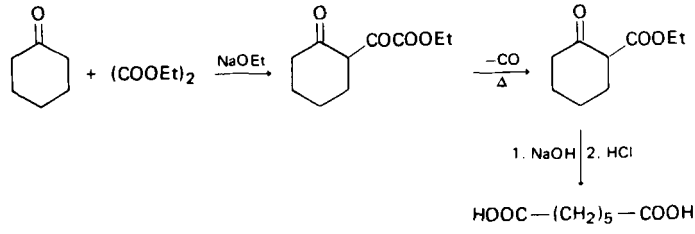
α-Anions of carboxylic acids have been found to act as Michael addends with α,β-unsaturated esters to produce half-esters of 1,5-pentanedioic acids (equation 48)[178].

$$(CH_3)_2\bar{C}COO + CH_2{=}CHCOOMe \xrightarrow[THF]{-78°C} \underset{(CH_3)_2CCOOH}{CH_2CH_2COOMe} \quad (48)$$

10. Claisen condensation

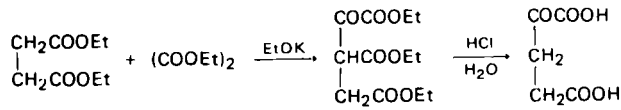
The Claisen condensation and its intramolecular counterpart, the Dieckmann reaction, are most frequently employed for the synthesis of β-keto esters and ketones[199]. However, both simple and crossed Claisen condensations have been used as key reactions in the preparation of certain carboxylic acids.

For example, pimelic acid[200] can be prepared from cyclohexanone and ethyl oxalate as shown in equation (49). The synthesis of α-ketoglutaric acid[201] is based



(49)

on initial crossed Claisen condensation of ethyl oxalate with diethyl succinate to give triethyl oxalylsuccinate, which is then hydrolysed and decarboxylated to yield the desired α-keto acid (equation 50). A recently reported method[202] for the synthesis of long-chain dicarboxylic acids involves utilization of the Claisen condensation. Thus, methyl *N,N*-dimethylsebacamate undergoes simple Claisen condensation to give *N,N,N',N'*-tetramethyl-9-carbomethoxy-10-oxononadecane diamide. Hydrolysis and decarboxylation affords 10-oxononadecanedioic acid, which is then converted to nonadecanedioic acid by Clemmensen reduction (equation 51).



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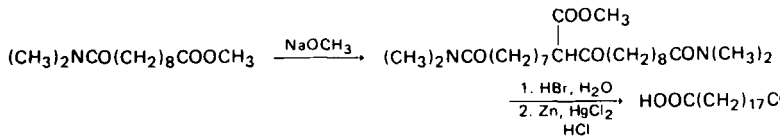
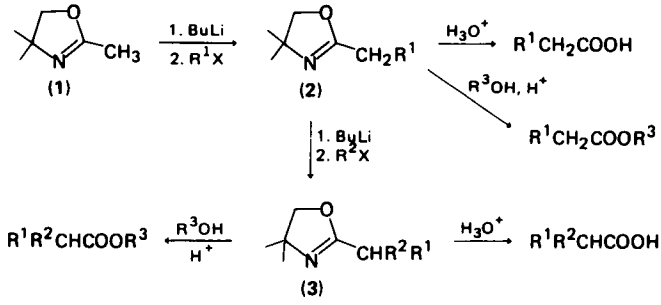


(51)

11. From oxazolines

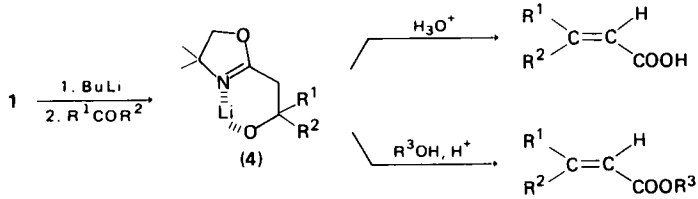
The use of heterocyclic starting materials is not often emphasized in general discussions of carboxylic acid synthesis. This problem has now been rectified by the appearance of an excellent review by Meyers[203], in which are described syntheses of acids, esters, amino acids, amides, peptides and nitriles from various heterocycles.

Among the numerous heterocyclic systems which can function as acid and ester precursors, 2-oxazolines have emerged as one of the most interesting and versatile[204]. The use of metalated 2-alkyl-2-oxazolines in the synthesis of carboxylic acids and esters is illustrated in Scheme 1[205]. Lateral lithiation of 2,4,4-trimethyl-2-oxazoline (1) with *n*-butyllithium at −78°C in THF, followed by alkylation of the resulting 2-lithiomethyl derivative, affords elaborated oxazolines



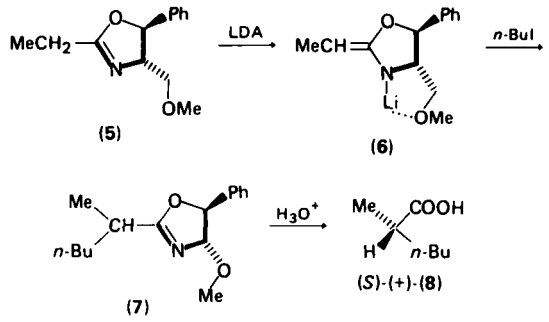
SCHEME 1.

2. Hydrolysis of 2 with aqueous hydrochloric acid then affords α-substituted acetic acids, while alcoholysis provides the corresponding esters. Sequential metalation and alkylation of 2 furnishes disubstituted oxazolines 3, which can be readily converted to α,α-disubstituted acids and esters by acid-catalysed hydrolysis and alcoholysis, respectively. It should be noted that cleavage of the oxazoline protecting group can also be effected under alkaline conditions using methyl iodide and aqueous sodium hydroxide[205]. Lithiation of 1 followed by sequential alkylation with 1,4-diiodopentane, lithiation, and a final hydrolysis step, affords a 2-methylcyclopentanecarboxylic acid as a *cis:trans* mixture containing 90% of the *cis* isomer[206]. If lithiation of 1 is followed by addition of an aldehyde or ketone to the reaction mixture, adducts of type 4 are produced (equation 52). Subsequent treatment of these intermediates with aqueous or alcoholic acid produces unsaturated acids and esters. Alcoholysis in the presence of very dilute mineral acid leads to formation of β-hydroxy esters[205].



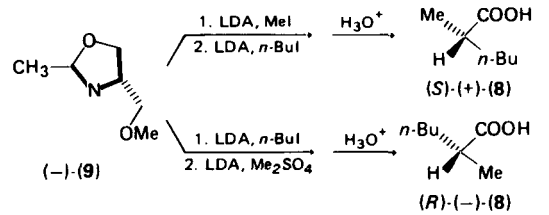
(52)

It is obvious that the synthesis of carboxylic acids via oxazoline-based routes closely resembles the α-anion approach to acid homologation. In fact, the latter procedure offers certain advantages in that starting materials are readily available and a final hydrolysis step is not necessary. However, the synthesis of chiral acids possessing high optical purity has been realized using chiral oxazolines[204,207-212], whereas the dianion method has not been employed in asymmetric synthesis. An example of such an asymmetric synthesis is illustrated in Scheme 2. In this sequence of reactions, chiral oxazoline (5), prepared by condensation of (1*S*, 2*S*)-(+)-1-phenyl-2-amino-1,3-propanediol with the imidate of propionitrile or ethyl orthopropionate, is used as the starting material. Reaction of 5 with LDA at −78°C produces lithio derivative 6, which, upon treatment with *n*-butyl iodide, affords alkylated oxazoline 7. Hydrolysis of 7 with aqueous hydrochloric acid then provides (*S*)-(+)-2-methylhexanoic acid (8) of 66–68% optical purity[211]. Perhaps the most significant aspect of the synthesis of chiral acids from oxazolines involves the separate preparation of both enantiomers of various α-alkylalkanoic acids from



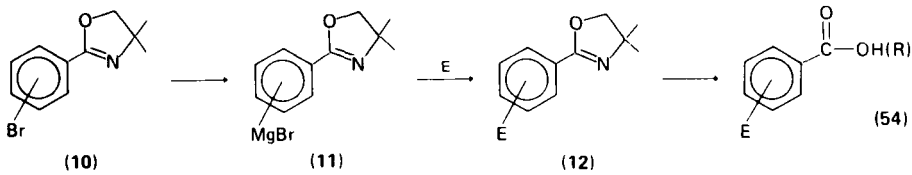
SCHEME 2.

a single chiral oxazoline[207,211]. Even more remarkable are the observations that the separate enantiomers can be prepared by varying the order of alkyl-group introduction, and that the absolute configuration of the resulting acids may be predicted prior to embarking on the synthetic scheme. Thus, introduction of the group of lower Cahn–Ingold–Prelog priority will produce acids with the (*S*) configuration, whereas initial introduction of the group of higher priority affords the acid possessing the (*R*) configuration. For example, metalation of (−)-**9** with LDA, methylation with methyl iodide, remetalation and alkylation with *n*-butyl iodide gives (*S*)-(+)-8 possessing 70–75% optical purity (equation 53). Alternatively, if the *n*-butyl group is introduced first, followed by methylation with methyl sulphate (methyl iodide is less satisfactory), hydrolysis of the resulting dialkylated oxazoline affords (*R*)-(−)-8 of 70% optical purity[211].



(53)

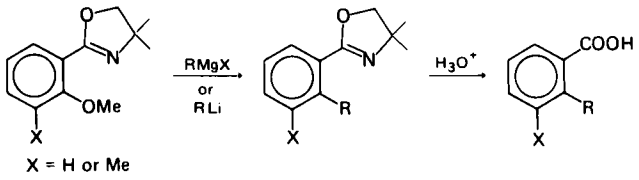
2-Aryl oxazolines have been used for the synthesis of substituted benzoic acids and esters. One such technique[213] (equation 54) involves conversion of bromo-



(54)

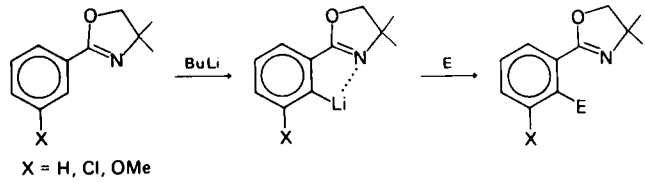
benzoic acids into the bromophenyloxazolines **10**, which are then reacted with magnesium to form Grignard reagents **11**. Condensations of **11** with various electrophiles, including aldehydes, ketones, epoxides, nitriles and deuterium oxide, produce substituted oxazolines **12**. Formation of substituted benzoic acids or benzoate esters is then accomplished by the usual methods of hydrolysis or

alcoholysis. In the case of 2-(*o*-methoxyphenyl) oxazoline the methoxy function is susceptible to nucleophilic displacement by either Grignard reagents or organolithium reagents. Completion of the reaction sequence by hydrolytic cleavage of the oxazoline masking group gives alkylbenzoic acids and diphenic acids (equation 55)[214].



(55)

Another possible application of aryloxazolines to acid synthesis is based on the finding that the oxazolinyl residue directs metalation of the aromatic ring to the *ortho* position, thereby producing a reactive site for elaboration of the aryl moiety[215]. For instance, treatment of aryl oxazolines with *n*-butyllithium affords *ortho* lithio derivatives, which react with various electrophiles (equation 56). Although hydrolysis to substituted benzoic acids was not carried out in this study, the synthetic potential is obvious.



(56)

12. Coupling reactions

Coupling reactions are defined here as reactions where a carbanionic species, usually an organometallic reagent, reacts with a haloester or haloacid to produce a new acid or ester. Such reactions differ from other methods discussed in this section in that the carboxy or carboalkoxy function of the product is furnished by the electrophilic component of the reaction rather than by the carbanion.

Grignard reagents undergo coupling reactions with THF-soluble chloromagnesium salts of ω-bromo acids in the presence of catalytic amounts of dilithium tetrachlorocuprate (equation 57)[216]. Carboxylic acid esters can be synthesized in a

$$RMgBr + Br(CH_2)_nCOOMgCl \xrightarrow[2.\ H_3O^+]{1.\ Li_2CuCl_4} R(CH_2)_nCOOH \qquad (57)$$

related fashion by reaction between copper(I) 'ate' complexes, formed from methylcopper(I) and primary or secondary Grignard reagents, and esters of primary iodoalkylcarboxylic acids[217]. For example, ethyl 21-docoseneoate can be prepared in 79% yield from methyl (10-undecenyl)cuprate and ethyl 11-iodoundecanoate

$$CH_2{=}CH(CH_2)_8CH_2Cl \xrightarrow[2.\ (MeCu(I))]{1.\ Mg,\ THF} CH_2{=}CH(CH_2)_8CH_2\overset{Me}{\underset{|}{C}}uMgCl$$

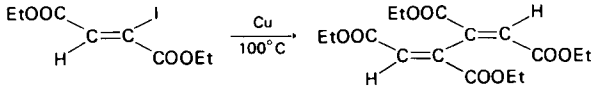
$$\xrightarrow[THF]{I(CH_2)_{10}COOEt} CH_2{=}CH(CH_2)_{19}COOEt \qquad (58)$$

(equation 58). Diarylcadmium reagents have been reported to undergo coupling with α-bromo esters to give phenylacetic esters (equation 59)[218]. α-Bromo esters undergo dimerization in the presence of zinc and copper(II) chloride to afford succinate esters (equation 60)[219]. Ullman-type coupling of diethyl iodofumarate

$$Ar_2Cd + BrCHRCOOEt \longrightarrow ArCHRCOOEt \tag{59}$$

$$R^1R^2\overset{Br}{\underset{|}{C}}HCOOR^3 \xrightarrow[THF]{Zn-CuCl_2} R^3OOC-\overset{R^1}{\underset{R^2}{C}}-\overset{R^1}{\underset{R^2}{C}}-COOR^3 \tag{60}$$

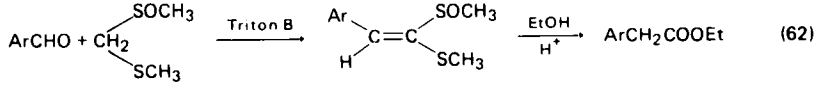
occurs with copper powder to afford pure *trans,trans*-1,2,3,4-tetracarboethoxy-1,3-butadiene in 96% isolated yield (equation 61)[220]. A similar reaction with diethyl iodomaleate affords 89% of the analogous butadiene consisting of 87% of the *cis,cis* ester and 13% of the *trans* isomer. Evidence was presented in this study to show that the products were formed by coupling of organocopper intermediates.



(61)

13. *Miscellaneous condensation reactions*

a. Carbanion reactions. Two recent synthetic methods involving carbanionic intermediates are worthy of note. In the first of these, the carbanion derived from the synthetically versatile reagent, methylsulphinylmethyl methyl sulphide (**13**)[221], is allowed to react with aryl aldehydes. The resulting 1-methylsulphinyl-1-methylthio-2-arylethylenes (**14**) afford α-substituted acetate esters upon ethanolysis (equation 62)[222]. A related procedure, also leading to α-substituted acetic acid esters, involves acylation of **13** with esters, followed by sodium borohydride reduction, acetylation, elimination and hydrolysis of the resulting unsaturated derivatives **14**[223].

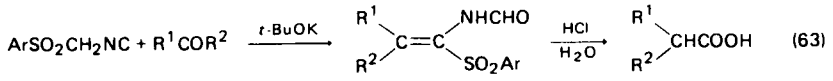


(62)

(**13**) (**14**)

The second procedure involves condensation of isocyanomethyl aryl sulphones (**15**) with aliphatic and aromatic aldehydes and ketones to give *N*-(1-arylsulphonyl-1-alkenyl) formamides (**16**), which can be hydrolysed to carboxylic acids containing one more carbon than the starting carbonyl compound (equation 63)[224,225].

Both of the foregoing methods provide a convenient route to saturated acids through active hydrogen condensations, whereas most related reactions

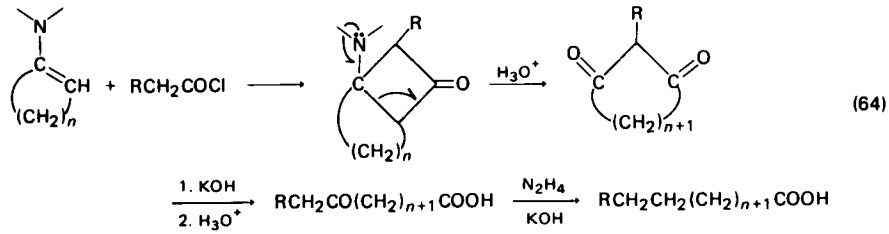


(63)

(**15**) (**16**)

(Knoevenagel, Doebner, Stobbe), involving active methylene components, afford unsaturated acids.

b. From enamines. A rather general method for the synthesis of long-chain acids involves reaction of enamines derived from cyclic ketones with an aliphatic acid chloride in the presence of the triethylamine. The resulting cyclobutanone derivative undergoes ring-opening during hydrolysis to form 2-alkyl-1,3-cycloalkanediones, which are then cleaved to keto acids. Reduction of the keto acids provides the saturated acid (equation 64)[226,227]. It should be noted that this scheme works best with enamines derived from cyclic ketones containing more than nine carbon atoms.



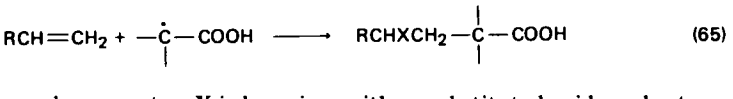
(64)

C. Acids by Free-radical Processes

The two types of radical reactions used most frequently for the synthesis of carboxylic acids involve either addition of radical species to unsaturated compounds or radical substitution on aromatic substrates. Radical additions represent the more versatile approach, and appear in subsequent sections of this chapter in connection with the preparation of other types of acid derivatives.

1. Radical additions to unsaturated systems

The use of radical additions for the synthesis of acids and acid derivatives has been reviewed[228]. The basic approach involves radical-chain addition of an α-carboxyalkyl radical to an olefinic substrate, to give an acid in which the nature of X depends upon the source of the radical addend (equation 65). If the radical is



(65)

generated from an α-bromo ester, X is bromine; with unsubstituted acids and esters, as well as α-chloro esters, X is hydrogen. Carboxyalkyl radicals are derived from carboxylic acids containing at least one α-hydrogen upon treatment with an appropriate initiator. The most efficient chemical initiators appear to be di-*t*-butyl peroxide (DTBP) and dibenzoyl peroxide (DBP), although several other peroxides of comparable thermal stability have been employed. The nature of the unsaturated component has a strong bearing on the success of these reactions, with terminal olefins serving as the most satisfactory acceptors for carboxyalkyl radical. Free-radical polymerization of other types of olefins may be a serious competing reaction.

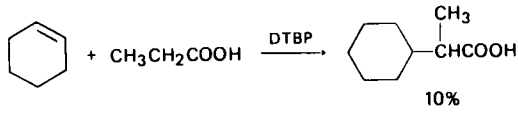
The general procedure employed for these reactions usually involves treatment of the olefin with a 10- to 100-fold molar excess of the carboxylic acid in the presence of a catalytic amount (ca 5–25 mol percent) of initiator at reflux. The

syntheses (equation 66) of *n*-decanoic acid[229,230], 2-methyldecanoic acid[231], 2,2-dimethyldodecanoic acid[231-233] and 2-cyclohexylpropanoic acid[234] are representative of the approach. Comparison of yields obtained in these reactions reveals the effect of both acid and olefin structure on the efficiency of the process.

$$n\text{-}C_6H_{13}CH{=}CH_2 + CH_3COOH \xrightarrow{DTBP} n\text{-}C_8H_{17}CH_2COOH \quad 60\text{–}70\% \tag{66a}$$

$$n\text{-}C_6H_{13}CH{=}CH_2 + CH_3CH_2COOH \xrightarrow{DTBP} n\text{-}C_8H_{17}\underset{\displaystyle CH_3}{\underset{|}{C}}HCOOH \quad 60\text{–}75\% \tag{66b}$$

$$n\text{-}C_8H_{17}CH{=}CH_2 + \underset{\displaystyle CH_3}{\underset{|}{C}}H_3CHCOOH \xrightarrow{DTBP} n\text{-}C_{10}H_{21}\underset{\displaystyle CH_3}{\underset{|}{C}}COOH \quad 36\% \tag{66c}$$



(66d)

2. *Carboxyalkylation of aromatic compounds*

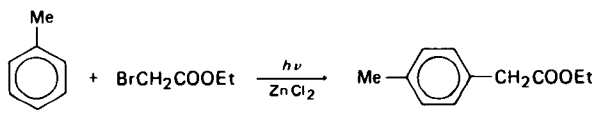
Generation of carboxymethyl radicals in the presence of suitable aromatic substrates results in homolytic substitution leading to arylacetic acids (equation 67). This process, which is referred to as aromatic carboxymethylation, has been the subject of a recent review[235].

$$Ar{-}H + \dot{C}H_2COOH \longrightarrow ArCH_2COOH \tag{67}$$

Carboxymethylations can be effected thermally with chloroacetic acid (in the presence of iron salts and/or potassium bromide), with bromoacetic acid, or with chloroacetylpolyglycolic acid. Thermally induced carboxymethylations proceed reasonably well with certain fused ring aromatics, but simple benzene derivatives do not react.

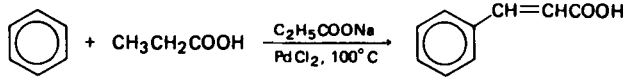
Oxidative carboxymethylation of aromatic compounds, including several mono- and disubstituted benzenes, has been accomplished using acetic acid or acetic anhydride as the radical source. Oxidizing agents which can be used to generate carboxymethyl radicals in such reactions include potassium permanganate, manganese(III) acetate, cerium(IV) acetate, diacetyl peroxide and DTBP.

Photochemical carboxymethylations have been employed in a limited number of cases. Satisfactory precursors for carboxymethyl radicals in these reactions include iodoacetic acid, thioglycolic acid and ethyl chloroacetate. Photochemical reactions appear to be the most satisfactory for carboxymethylation of simple aromatics. For example ethyl *p*-methylphenylacetate can be prepared from toluene and ethyl bromoacetate by photolysis in the presence of zinc chloride (equation 68)[236].



(68)

Aromatic carboxyvinylation can be realized in moderate yields by reacting aliphatic acids possessing α- and β-hydrogens with an appropriate aromatic substrate in the presence of palladium(II) salts and alkali metal carboxylates[237]. For example, treatment of benzene with propionic acid and sodium propionate in the presence of palladium(II) chloride gives cinnamic acid in 28% yield (equation 69).

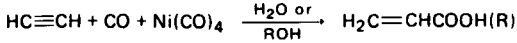


(69)

D. Acids by Hydrocarboxylation Reactions

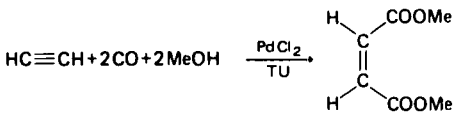
Hydrocarboxylations are classified here as reactions in which the –COOH group is introduced by treatment of organic molecules with carbon monoxide in the presence of an appropriate catalyst. Although such reactions have been valued primarily for their industrial applications, recent developments in the area of transition metal catalysis now permit hydrocarboxylations to be carried out at ambient temperatures with low carbon monoxide pressure. Several excellent reviews summarizing reactions of carbon monoxide with various organic compounds have appeared[238-241]. One of these[240] is devoted specifically to the synthesis of carboxylic acids and esters under mild conditions. The present discussion is meant to outline some of the more important hydrocarboxylation procedures which can be conducted under normal laboratory conditions. Since preparations of acids and esters are generally quite similar, both types of compounds are discussed here.

Acetylenes and olefinic compounds readily yield to hydrocarboxylation, affording unsaturated and saturated acids (esters), respectively. For example the Reppe synthesis[242] of acrylic acid and its esters is accomplished by reaction of acetylene with carbon monoxide in the presence of nickel tetracarbonyl and water, or a mixture of water and alcohol (equation 70). Treatment of acetylene with



(70)

carbon monoxide using palladium chloride complex with thiourea (TU) in methanol affords dimethyl maleate in excellent yield (equation 71)[243]. Although hydrocarboxylation of substituted acetylenes may lead to complications[238-241] too numerous to mention in this review, it is possible in some instances to effect reasonably good regiospecificity in the production of unsaturated acids as illustrated in equation (72)[244].



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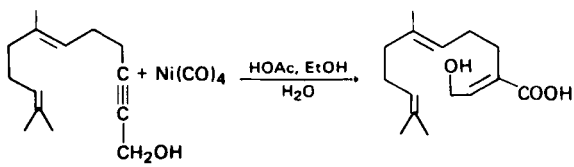
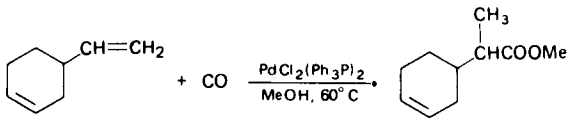


(72)

Olefinic substrates normally require more rigorous conditions for hydrocarboxylation than alkynes. However, the synthesis of acids from olefins can be effected smoothly at atmospheric pressure and room temperature using nickel tetracarbonyl in the presence of organic acids (equation 73)[245]. Olefins can also be carbonylated at low temperature employing palladium chloride complexed with triphenylphosphine[246] as shown for 4-vinylcyclohexene (equation 74). However,

$$RCH{=}CH_2 + CO + H_2O \xrightarrow[R^1COOH]{Ni(CO)_4} \underset{\text{major}}{RCH(CH_3)COOH} + \underset{\text{minor}}{RCH_2CH_2COOH} \quad (73)$$



(74)

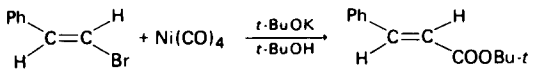
these reactions require carbon monoxide pressures of 300–700 atmospheres. Recently[247-248], linear, rather than branched, esters have been obtained by carbonylation of α-olefins using ligand-stabilized platinum(II)–group 4B metal halide complexes[247] or ligand-stabilized palladium(II)–group 4B metal halide complexes[248]. In spite of the high degree of regiospecificity, these reactions also require rather high (>100 atm) carbon monoxide pressures. Carbonylation of olefins can be carried out at room temperature and atmospheric pressure using a copper(I) carbonyl catalyst in concentrated sulphuric acid[249]. These processes give mixtures of tertiary acids resulting from extensive rearrangement of the carbonium ions formed in the reaction medium.

Organic halides furnish carboxylic acids and esters upon carbonylation. Allylic halides can be converted to β,γ-unsaturated esters by treatment with carbon monoxide in the presence of nickel π-allyl complexes (equation 75)[250]. Benzylic

$$CH_2{=}C(CH_3)CH_2Cl + CO + MeOH \xrightarrow[\text{complex}]{Ni\ \pi\text{-allyl}} CH_2{=}C(CH_3)CH_2COOMe \quad (75)$$

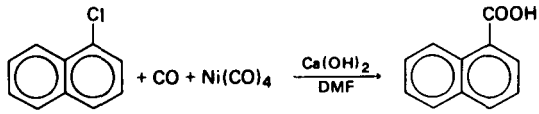
halides are transformed into phenylacetic acids and esters in good yields by nickel tetracarbonyl-catalysed carbonylation in DMF if iodide ion and a basic reagent, such as calcium oxide or triethylamine, are present (equation 76)[251]. Vinyl halides can be carbonylated to form α,β-unsaturated esters with retention of stereochemistry about the double bond by means of nickel tetracarbonyl in *t*-butyl alcolol containing potassium *t*-butoxide (equation 77)[252], or in methanol containing sodium methoxide[253]. These reactions do not require addition of exogeneous carbon monoxide.

$$PhCH_2Cl + CO + H_2O \xrightarrow[CaO,\ DMF]{Ni(CO)_4,\ I^-} PhCH_2COOH \quad (76)$$



(77)

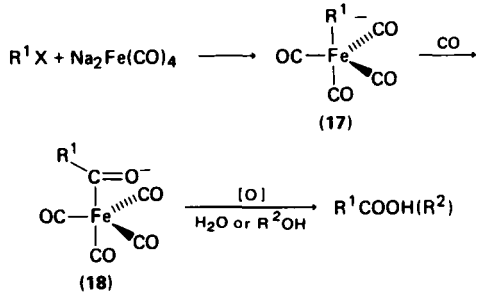
A recent example of facile hydrocarboxylation of aryl halides involves reactions employing nickel tetracarbonyl and calcium hydroxide in polar aprotic solvents



(78)

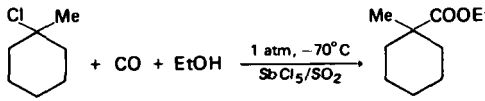
(equation 78)[254]. Aryl and vinylic bromides and iodides as well as benzyl chloride react with carbon monoxide and alcohols in the presence of tertiary amines and palladium–triphenylphosphine to form esters in good yields[255]. Simple alkyl halides and/or tosylates with sodium tetracarbonyl ferrate(−II) to give alkyltetracarbon monoxide and cobalt carbonyl anion in methanol containing a tertiary amine base[256].

An interesting procedure[257] leading to acids and esters is based on treatment of halides and/or tosylates with sodium tetracarbonyl ferrate(−II) to give alkyltetracarbonyliron(I) complexes (17), which react with carbon monoxide to afford acyl complexes (18) (equation 79). Oxidation of either type complex with oxygen or aqueous sodium hypochlorite affords acids in good yield. When oxidation is carried out in alcohol solution the corresponding esters are obtained.



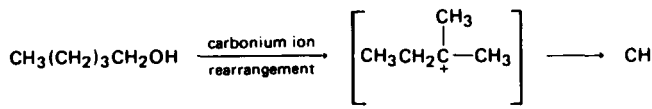
(79)

Carbonylation of tertiary alkyl halides can be effected with carbon monoxide in liquid SO_2 using antimony pentafluoride (equation 80)[258].



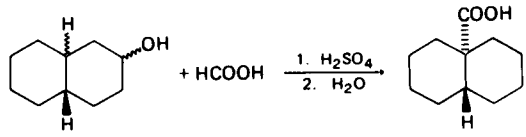
(80)

Alcohols can serve as useful starting materials for carboxylic acids under reaction conditions favouring carbonium ion formation. It should be noted that in many such reactions, rearrangement of the initially generated primary and secondary carbonium ions occurs to give tertiary carboxylic acids and esters. For example, treatment of 1-pentanol in 98% sulphuric acid with carbon monoxide in the presence of copper(I) oxide affords 2,2-dimethylbutanoic acid as the major product (equation 81)[259]. Similarly, 2-hydroxydecalin yields *trans*-9-decalincarboxylic acid



(81)

upon treatment with formic acid in concentrated sulphuric acid at 0°C (equation 82)[260,261]. This conversion is an example of the Koch–Haaf reaction[262,263] in



(82)

which an alcohol or alkene serves as the carbonium ion precursor, and formic acid is the source of carbon monoxide. A recent report describes the hydrocarboxylation of alcohols using carbon monoxide in the presence of hydrogen fluoride and antimony pentafluoride[264].

An interesting method for the synthesis of *N*-acylamino acids is based on carbonylation of *N*-(hydroxymethyl)-amides or imides with carbon monoxide or formic acid in sulphuric acid[265,266]. The preparation of hippuric acid is illustrative of this procedure (equation 83).

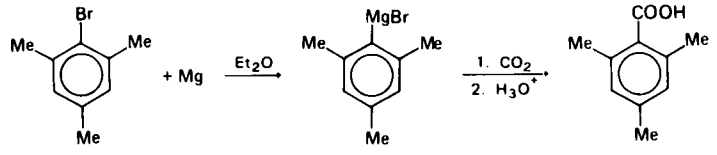
$$PhCONHCH_2OH + CO \xrightarrow[2.\ H_2O]{1.\ H_2SO_4,\ HOAc} PhCONHCH_2COOH \qquad (83)$$

Alkanes containing tertiary hydrogens can be carbonylated by allowing them to react with formic acid or carbon monoxide and an alcohol or alkene in sulphuric acid. The alcohol or alkene is converted to a carbonium ion which then abstracts a hydride ion from the alkane to form a new cation. This cation reacts with carbon monoxide to yield the acid derived from the saturated substrate. 1-Adamantanecarboxylic acid[267] is synthesized in this way. Carbonylation of saturated hydrocarbons has also been accomplished with carbon monoxide and an alkene or alcohol in sulphuric acid using copper(I) carbonyl as the catalyst[268].

E. Acids by Carbonation of Organometallic Reagents

Reaction of organometallic reagents with carbon dioxide is a versatile and widely used method for carboxylic acid synthesis. Fundamental considerations of this method, along with numerous examples of its application to the synthesis of mono- and dicarboxylic acids, have been reviewed[269].

Of the numerous types of organometallics which can be carbonated to form acids, Grignard reagents and organolithium reagents are used most frequently because of the facility with which they can be prepared by halogen–metal exchange or by direct metalation (equation 84)[270,271]. The syntheses of mesitoic acid[272] and pentachlorobenzoic acid (equation 85)[273] represent typical Grignard



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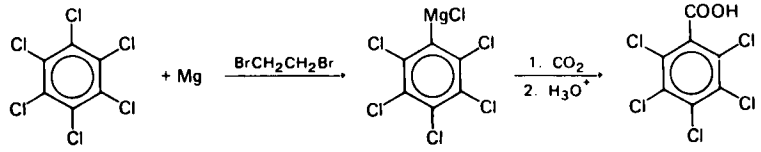
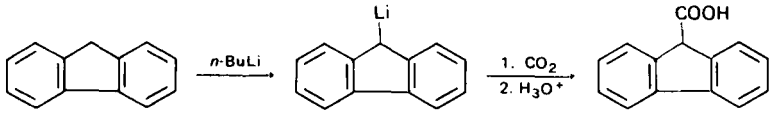
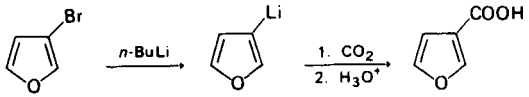


(85)

carbonations. The use of ethylene bromide, as shown in equation (85), accelerates the formation of Grignard reagents from aryl chlorides. The synthesis of fluorene 9-carboxylic acid is representative of the formation and carbonation of organolithium reagents derived from acidic hydrocarbons (equation 86)[274]. The recently reported preparation of 3-furoic acid[275] is typical of the procedures used to prepare aromatic acids from aryl halides via initial halogen–metal exchange (equation 87).

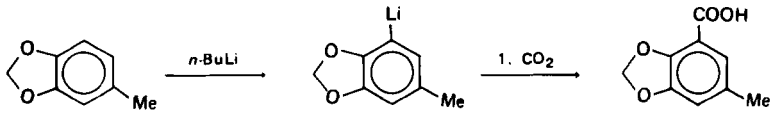


(86)



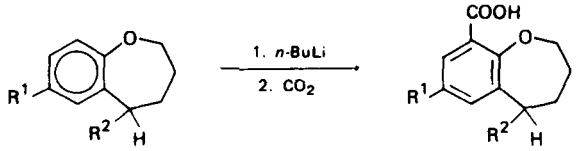
(87)

Aryllithium reagents suitable for carbonation can also be prepared by direct ring metalation of benzene derivatives containing one or more alkoxyl functions. Lithiation is directed exclusively *ortho* to the ether function. Equations (88)–(90) are typical of *ortho* lithiation followed by carbonation. Note that lithiation of 3,5-dimethoxyfluorobenzene is accompanied by replacement of fluorine.

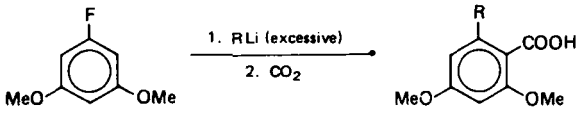


(Ref. 276)

(88)



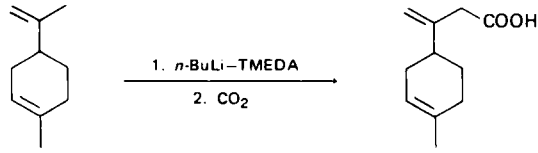
(Ref. 277) (89)



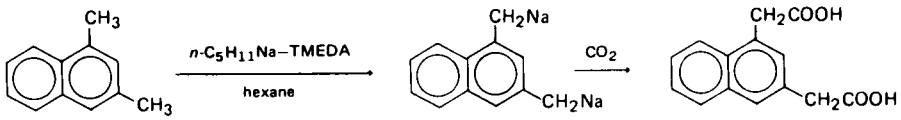
(Ref. 278) (90)

An interesting development associated with the preparation of organolithium reagents for carbonation is the discovery that certain alkenes undergo allylic lithiation by means of the powerful metalating agent formed by complexation of *n*-butyllithium with *N,N,N',N'*-tetramethylethylenediamine (TMEDA)[279]. Thus, treatment of limonene with *n*-butyllithium–TMEDA followed by carbonation produces the β,γ-unsaturated acid derived from lithiation at $C_{(10)}$ (equation 91)[280]. Although the generality of this approach has yet to be fully determined, it would appear to offer a decided advantage over more conventional methods for allylic metalation, which usually employ organosodium reagents[281,282].

Recently, it has been found that dimethylarenes such as 1,3-dimethylnaphthalene can be dimetalated with *n*-amylsodium complexed with TMEDA to produce disodio derivatives, which are carbonated to form dicarboxylic acids (equation 92)[283].

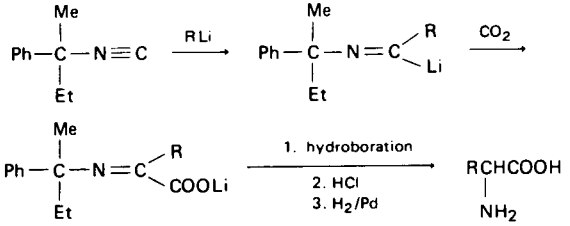


(91)



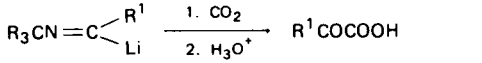
(92)

Carbonation of lithium aldimines, formed by addition of alkyllithium reagents to isocyanides, produces α-imino acids, which can be reduced and debenzylated to afford α-amino acids (equation 93)[284]. Use of optically active isocyanides leads to



(93)

production of amino acids of reasonably high optical purity. In a related series of reactions, lithium aldimines have been carbonated, and the intermediate α-imino acids hydrolysed to α-keto acids (equation 94)[285]. Reaction of organolithium reagents with isocyanides containing α-hydrogens results in formation of α-lithio derivatives, which can be carbonated to give *N*-formyl α-amino acids. Subsequent hydrolysis of the *N*-formyl group produces free amino acids (equation 95)[286].



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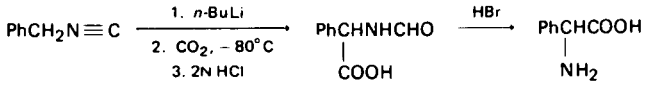
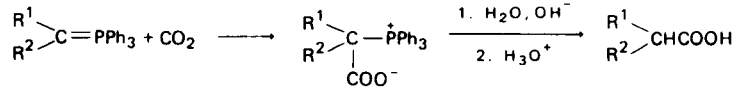


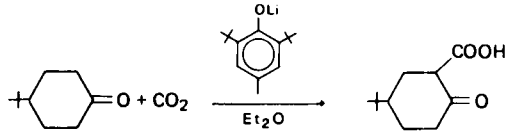
(95)

Carbonation of phosphoranes represents an efficient new method for acid preparation (equation 96)[287].



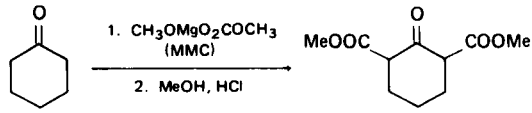
(96)

The synthesis of β-keto acids by carbonation of ketones can be effected in good yields using the hindered base, lithium 4-methyl-2,6-di-*t*-butylphenoxide (equation 97)[288]. This reagent is also useful for carbonation of acetylenes and sulphones[288]. Iron(III) ethoxide in DMF has also been found to be an effective base for α-carbonation of ketones[289].

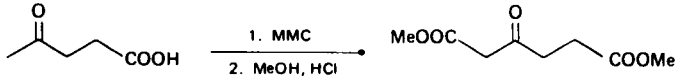


(97)

Several recent reports have further confirmed the utility of methyl magnesium carbonate[290] (MMC) as an excellent reagent for carboxylation of carbonyl compounds, including cyclohexanone (equation 98)[290], levulinic acid (equation 99)[291], and γ-butyrolactones (equation 100)[292]. γ- and δ-Lactones also undergo α-carboxylation upon treatment with LDA in THF at −78°C, followed by addition of carbon dioxide to the reaction mixtures[293].



(98)



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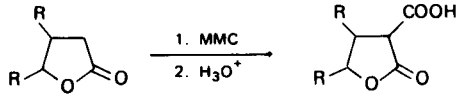


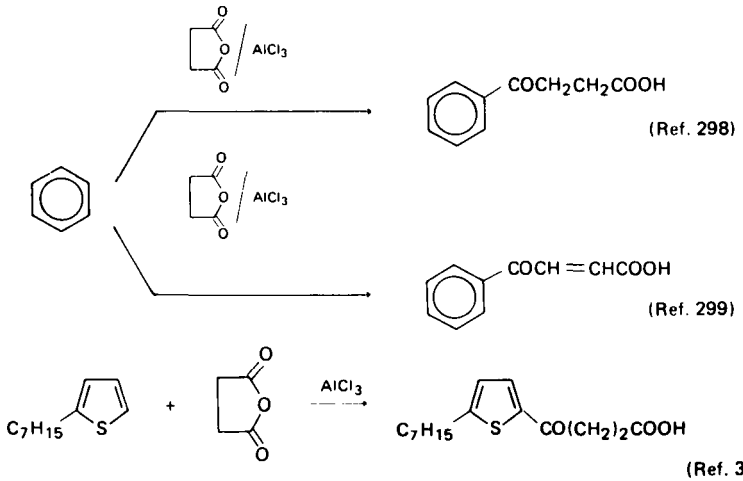
(100)

Ring carboxylation of alkali metal salts of resorcinol and α-naphthol can be accomplished with carbon dioxide under conditions of the Kolbe–Schmitt reaction[294]. An interesting modification of this reaction employs MMC as the carboxylating agent[295]. Carboxylation of certain aromatic systems has been realized using the mixture acetic acid–acetic anhydride–sodium acetate in the presence of palladium chloride[296].

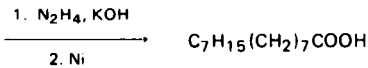
F. Acids by Electrophilic Substitution Reactions

A classical method of acid synthesis by electrophilic substitution involves acylation of an appropriate aromatic substrate with a dibasic acid anhydride in the presence of a Lewis acid catalyst[114,115]. Several typical examples are shown in equations (101) and (102). The last of these includes both reduction of the ketone function, a common procedure for synthesizing ω-aryl acids, and reductive desulphurization of the thiophene ring, a useful method for homologation of carboxylic acids.

Aromatic acids and esters can be prepared by Friedel–Crafts-type reactions using various derivatives of carbonic acid[301]. For example, reaction of mesitylene

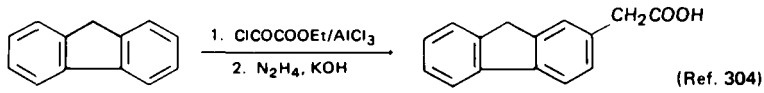


(101)



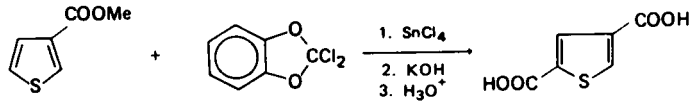
(102)

with oxalyl chloride in the presence of aluminium chloride yields mesitoic acid[302]. Phosgene[303] can also be used to prepare benzoic acids, while ethyl oxalyl chloride affords α-keto acids, which can be converted to arylacetic acids by reduction (equation 103)[304]. Pyrocatechol dichloromethylene acetal[305] is a useful reagent

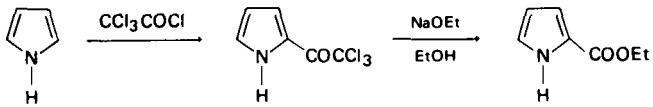


(103)

for introduction of aromatic carboxyl groups, as illustrated in the synthesis of 2,4-thiophenedicarboxylic acid (equation 104)[306]. Trichloroacetyl chloride reacts with pyrrole to give 2-trichloroacetylpyrrole, which can then be converted to the ethyl ester of 2-pyrrolecarboxylic acid by treatment with sodium ethoxide (equation 105)[307].



(104)



(105)

G. Acids by Oxidation Reactions

The preparation of acids and esters can be accomplished by the oxidation of a number of functional groups using a wide variety of reagents. In this section the

preparation of acids and esters is primarily categorized in terms of the functionality of the starting material and subsequently in terms of the oxidizing agent used. Since two comprehensive discussions of the oxidation mechanisms using a wide variety of oxidizing agents has been published[308,309], a detailed discussion of this aspect of the oxidation will not be attempted in this review.

1. *Oxidation of alcohols*

Only one general review[310] has been published on the oxidation of alcohols and it is specifically concerned with *Phenyl Derivatives of Dihydric and Polyhydric Alcohols and Their Oxidation Products.*

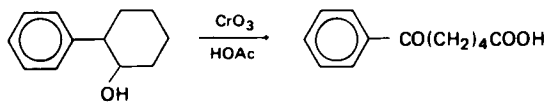
a. With base. Although not considered a major reaction for the oxidation of alcohols to acids, treatment of alcohols with base at high temperature has been reported to oxidize alcohols to acid in good to excellent yields in at least two cases[311,312]. In the oxidation of hydrocinnamyl alcohol-d to hydrocinnamic acid-d, treatment with KOH at 245–255°C followed by acidification was used to effect the conversion in 88% yield[311]. Sodium hydroxide at 340–360°C and 50–500 atm has been used[312] to convert terminal alkanediols into sodium alkane dicarboxylates in yields ranging from 50 to 75% (equation 106).

$$HOCH_2-CH_2OH + NaOH \xrightarrow[\substack{300°C\\400\ atm}]{heat} \underset{75\%}{Na^+\,\bar{O}OC-C\bar{O}O\,Na^+} \qquad (106)$$

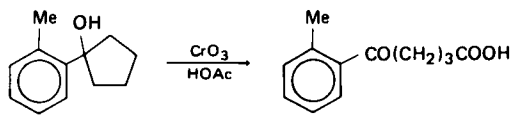
b. With hypochlorite. A rather interesting oxidation is the reaction of an excess of isoamyl alcohol with *t*-butylhypochlorite in carbon tetrachloride which leads to an 89% yield of isoamylisobutylate (equation 107)[313].

$$Me_2CHCH_2CH_2OH + Me_3COCl \xrightarrow{CCl_4} Me_2CHCH_2COOCH_2CH_2CHMe_2 \qquad (107)$$

c. With oxides of chromium. The oxides of chromium in a variety of solvents have been one of the most common oxidizing systems used to convert alcohols to acids. Chromium trioxide in acetic acid has been used to effect the conversion of 10-fluorodecanol to 10-fluorodecanoic acid[314], 1-phenyl-1-cyclohexanol to δ-benzoylvaleric acid (equation 108)[315,316] and 1-(*o*-tolyl)cyclopentanol to γ-(2-methylbenzoyl)butyric acid (equation 109)[317].



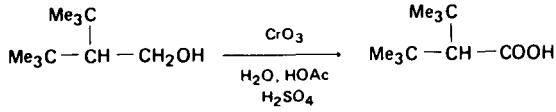
(108)



(109)

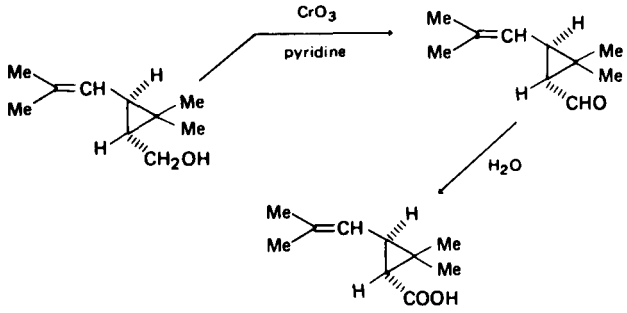
When chromium trioxide is dissolved in water and acetic acid is added the resulting oxidizing agent is chromic acid. This reagent has been used in sulphuric acid, to convert 2,2-di-*t*-butylethanol into di-*t*-butylacetic acid (equation 110)[318], and in acetone, to convert the isomeric tetrahydropyranyloxy-2,2,4,4-

tetramethylcyclobutan-1-carbinols into their corresponding isomeric hydroxy acids[319]. This reaction represents a unique cleavage of a hydroxy protecting group without additional oxidation.



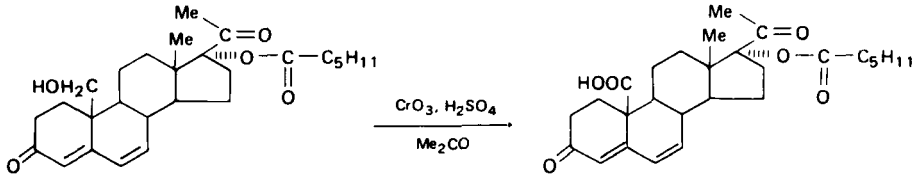
(110)

One indication of the difference in oxidizing ability of chromium trioxide and chromic acid can be seen from the work of Mills, Murray and Raphael[320], who found that oxidation of chrysanthemyl alcohol at room temperature with chromium trioxide in dry pyridine afforded the corresponding aldehyde; however, upon the addition of water, the oxidation process was allowed to continue further to produce (±)-*trans*-chrysanthemic acid (equation 111). Similar oxidation of the allenic alcohol, 2,2-dimethyl-3-(2-methylprop-1-enylidene)cyclopropylmethanol, afforded dehydrochrysanthemic acid[320].



(111)

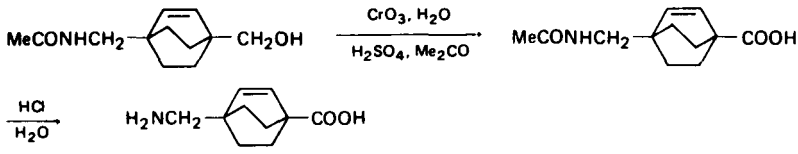
Addition of chromium trioxide to water and sulphuric acid produces Jones' reagent, which has been used in acetone to effect the oxidation of the steroid shown in equation (112) to its corresponding acid[321], and of 1-acetamidomethyl-4-hydroxymethylbicyclo[2.2.2]oct-2-ene to 4-acetamidomethylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, which upon hydrolysis with hydrochloric acid affords 4-aminomethylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid (equation 113)[322].



(112)

t-Butyl chromate has been used to oxidize hexadecanol to hexadecanoic acid in 54% yield[323].

With sodium dichromate as the oxidizing agent it is very common to find an ester as the product of alcohol oxidation, as in the oxidation of *n*-butyl alcohol which affords *n*-butyl *n*-butyrate (equation 114)[324].



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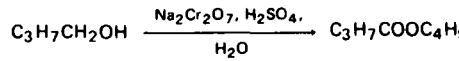
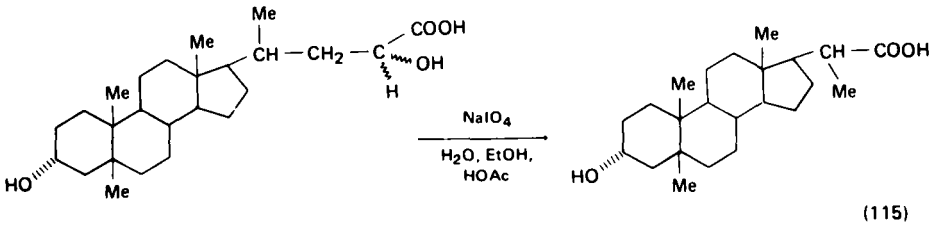


(114)

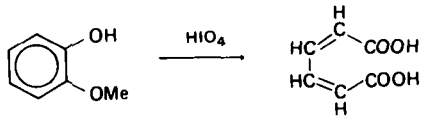
d. With periodic acid and periodates. The use of metaperiodic acid (HIO_4), sodium metaperiodate ($NaIO_4$) and paraperiodic acid (H_5IO_6) as oxidizing agents in organic and bio-organic chemistry has recently been reviewed[325].

Periodate oxidative cleavage of the α-hydroxy acid side-chain in the bile acid 3α,22-dihydroxycholanic acid in a water–ethanol–acetic acid solution affords norcholanic acid (equation 115)[326].



(115)

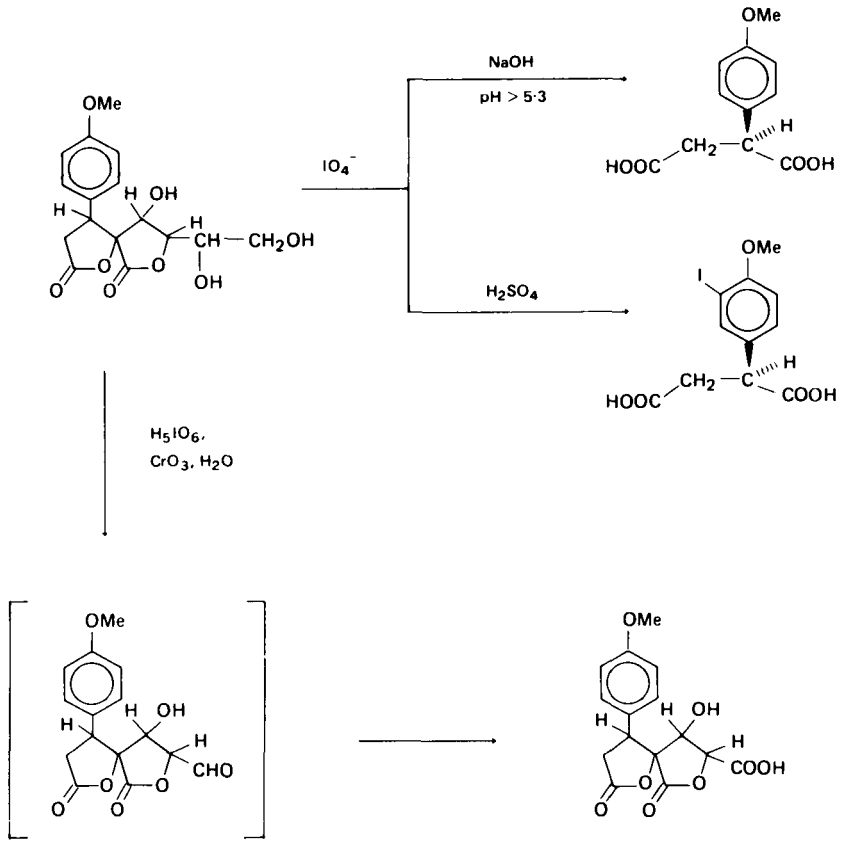
The reaction of periodic acid itself as an oxidizing agent has also been reported. With guaiacol the reaction has been reported[327] to yield *o*-benzoquinone and *cis,cis*-muconic acid, obtained by further cleavage of the *o*-benzoquinone initially formed (equation 116).



(116)

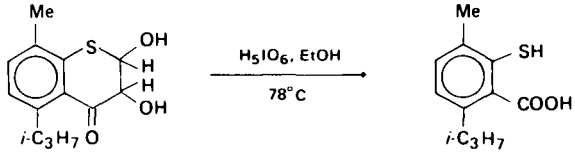
Application of periodate and periodic acid oxidations to the field of natural products is exemplified by the work of Perold and coworkers[328], (Scheme 3) who treated the dilactone canocarpin methyl ether (naturally occurring from the dried leaves of *Leucospermum conocarpodendron*, South Africa) with sodium periodate at pH >5.3 and with orthoperiodic acid in sulphuric acid. The dilactone, which has the 4*S*, 5*S*, 8*R*, 9*R*, 10*S* configuration, was found to have four of its chiral centres destroyed during the reaction and gave (+)-*p*-methoxyphenylsuccinic acid with a 4S configuration at pH >5.3 using sodium periodate, and (+)-(3-iodo-4-methoxyphenyl)succinic acid under acid conditions using orthoperiodic acid. However, when the same compound was oxidized with a mixture of paraperiodic acid and chromium trioxide in water, the primary–secondary glycol function was degraded to the carboxy group in 85% yield via an intermediate aldehyde[329]

An example of oxidative thio ring-opening using paraperiodic acid has been reported[330] in a preparation of a mercaptocumenecarboxylic acid. Refluxing a solution of 2,3-dihydro-2,3-dihydroxy-5-isopropyl-8-methyl-1-thianaphthalene-4-



SCHEME 3.

one with paraperiodic acid in 95% ethanol afforded a crude product which was warmed for two hours with aqueous 10% sodium hydroxide to give 3-mercapto-4-methyl cumene-2-carboxylic acid in 87% yield.



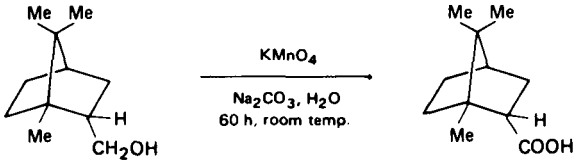
(117)

e. With oxides of manganese. Both acidic and basic solutions of potassium permanganate have been used successfully to oxidize alcohols to carboxylic acids. For example, reaction of 5,5,5-trichloropentanol with an acidic solution of potassium permanganate afforded δ,δ,δ-trichloropentanoic acid in 92% yield[331] while treatment of isobutyl alcohol with basic potassium permanganate afforded isobutyric acid in 84% yield (equation 118)[332]. This method has also been used to

$$Me_2CHCH_2OH \xrightarrow[Na_2CO_3]{KMnO_4} Me_2CHCOOH \qquad (118)$$

prepare[332] *n*- and *iso*-valeric, *n*-hexoic, *n*-heptoic and enanthylic acids from their corresponding alcohols.

Bicyclic systems have also been oxidized using potassium permanganate without destruction of the bicyclic skeleton, as illustrated by the room-temperature conversion of *endo*-2-hydroxymethylbornane to *endo*-2-bornane carboxylic acid in 66% yield using a sodium carbonate solution of permanganate[333].

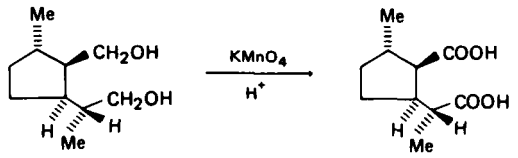


(119)

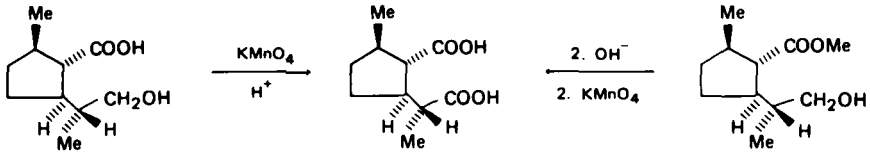
Silanes have also been oxidized using potassium permanganate without any destruction of the silicon–carbon bond, as indicated by the conversion of dimethyl bis(3-hydroxypropyl)silane to its corresponding dibasic acid (equation 120)[334].

$$Me_2Si(CH_2CH_2CH_2OH)_2 \xrightarrow{KMnO_4} Me_2Si(CH_2CH_2COOH)_2 \qquad (120)$$

That alcohols can be oxidized to carboxylic acids using potassium permanganate in acid or base without effecting the stereochemistry of the molecule is illustrated by the work of Ficini and Angelo[335], shown in equations (121) and (122).

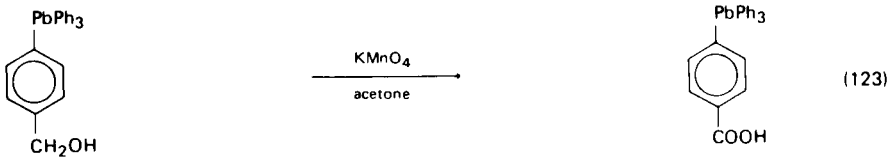


(121)

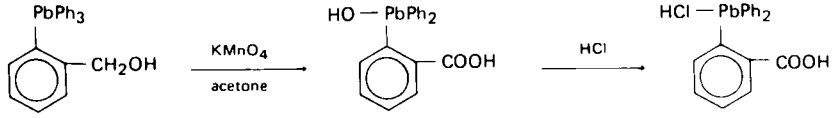


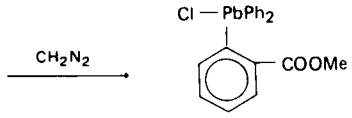
(122)

The use of potassium permanganate oxidation of alcohols to acids has been extended to organometallic systems with interesting results[336]. Permanganate oxidation of (*p*-hydroxymethylphenyl)triphenyllead in acetone gave (*p*-carboxyphneyl)triphenyllead in 25% yield (equation 123). However, treatment of (*o*-hydroxymethylphenyl)triphenyllead with permanganate in acetone (equation 124) not only effected oxidation of the hydroxymethyl group to carboxyl, but in addition one phenyl group was cleaved and replaced by hydroxyl, giving (*o*-carboxyphenyl)diphenyllead hydroxide. Upon reaction with hydrogen chloride, the hydroxide formed (*o*-carboxyphenyl)diphenyllead chloride which was con-



(123)



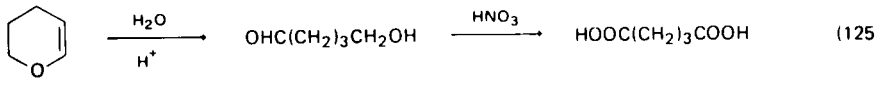


(124)

verted to its methyl ester by reaction with diazomethane. No pure product was isolated from similar oxidation attempts of the *m*-hydroxymethyl compound.

f. With oxides of nitrogen. The most common oxide of nitrogen used to convert alcohols to carboxylic acid is nitric acid. This reagent has been used to prepare substituted carboxylic acids from substituted alcohol starting materials in good yields; for example, β-chloropropionic acid in 78–79% yield from trimethylene chlorohydrin[337], and 6-bromohexanoic acid in 80% yield from 6-bromo-1-hexanol[338].

Nitric acid has also been used to prepare various dicarboxylic acids from a variety of starting materials. Glycols containing 5–9 carbons have been oxidized with 57% nitric acid at 95–105°C to give 40–50% yields of the corresponding dicarboxylic acids[339]. Treatment of cyclohexanol with 50% nitric acid afforded a 58–60% yield of adipic acid[340], while acid hydrolysis of dihydropyran followed by nitric acid oxidation of the resulting aldehyde gave a 70–75% yield of glutaric acid (equation 125)[341].



(125)

The only other oxide of nitrogen which has been used extensively for the oxidation of alcohols to acids has been dinitrogen tetraoxide. This reagent has been used at low temperatures to prepare[342] good yields of mono- and dicarboxylic acids from a variety of alcohols and glycols (Table 1).

g. With other oxides of metals. Aside from the metal oxides already discussed above, several other metal oxides have been found to be useful for both specific and general oxidation of alcohols to carboxylic acids.

The use of nickel peroxide[343,344] in the oxidation of organic compounds has recently been reviewed[345] and the reader is referred to this work for specific examples of the use of this reagent.

TABLE 1. Preparation of carboxylic acids from alcohols and glycols using nitrogen tetraoxide

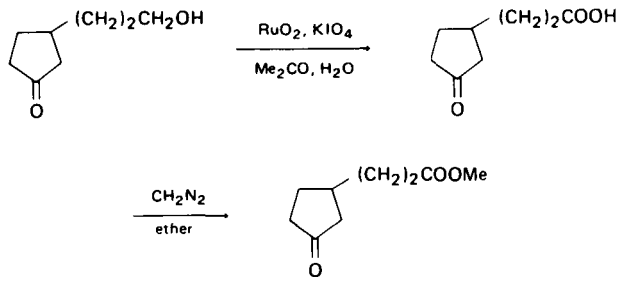
Starting material	Product	Yield (%)
$Me(CH_2)_4CH_2OH$	$Me(CH_2)_4COOH$	80
$Me(CH_2)_6CH_2OH$	$Me(CH_2)_6COOH$	83
$Me(CH_2)_8CH_2OH$	$Me(CH_2)_8COOH$	85
$Me(CH_2)_{10}CH_2OH$	$Me(CH_2)_{10}COOH$	86
$Me(CH_2)_{12}CH_2OH$	$Me(CH_2)_{12}COOH$	90
$Me(CH_2)_{14}CH_2OH$	$Me(CH_2)_{14}COOH$	90
$Me(CH_2)_{16}CH_2OH$	$Me(CH_2)_{16}COOH$	95
$PhCH_2OH$	PhCOOH	19
$PhCH_2CH_2OH$	$PhCH_2COOH$	63
$PhCH_2CH_2CH_2OH$	$PhCH_2CH_2COOH$	85
$HOCH_2CH_2CH_2CH_2OH$	$HOOCCH_2CH_2COOH$	81
$HOCH_2(CH_2)_3CH_2OH$	$HOOC(CH_2)_3COOH$	73
$HOCH_2(CH_2)_4CH_2OH$	$HOOC(CH_2)_4COOH$	96
$HOCH_2(CH_2)_5CH_2OH$	$HOOC(CH_2)_5COOH$	91

Electrolytic oxidation using silver oxide under neutral or mildly alkaline conditions has been reported[346] to afford good yields of carboxylic acids from a variety of alcohols (Table 2). The only alcohol which was reported to give no reaction upon treatment with this reagent was *p*-nitrobenzyl alcohol.

Although ruthenium tetroxide is a powerful oxidizing agent it is not commonly used to oxidize alcohols to acids. Treatment of primary alcohols with this reagent usually affords mixtures of aldehydes and acids or acids alone in low yields, as indicated by the conversion of *n*-hexyl alcohol to caproic acid in 10% yield[347]. However, sodium or potassium ruthenate has been used successfully in converting alcohols to acids. This reagent, which is normally prepared by the reaction of ruthenium dioxide with sodium or potassium metaperiodate, has been used to oxidize 3-(3-hydroxypropyl)cyclopentanone to β-(3-oxocyclopentyl)propionic acid in 60% yield (equation 126)[348]. The acid was converted to methyl β-(3-oxocyclopentyl)propionate upon reaction with diazomethane. Other successful conversions[349] have included: benzyl alcohol to benzoic acid in 97% yield, cinnamyl alcohol to cinnamic acid in 70% yield and, cinnamic acid into benzoic acid in 91% yield.

TABLE 2. Preparation of carboxylic acids from alcohols via electrolytic oxidation

Starting alcohol	Acid product	Yield (%)
Ethanol	Acetic acid	100
n-Propanol	Propionic acid	100
1-Butanol	*n*-Butyric acid	99
2-Ethylbutanol-1	2-Ethylbutanoic acid	33
1-Pentanol	*n*-Pentanoic acid	100
3-Methylpentanol-1	3-Methylpentanoic acid	100
1-Hexanol	*n*-Hexanoic acid	35
2-Ethylhexanol	2-Ethylhexanoic acid	100
1-Octanol	*n*-Octanoic acid	22
Benzyl alcohol	Benzoic acid	60



(126)

h. With air, oxygen and/or peroxides. The effective use of air as an oxidizing agent to effect conversion of alcohols to acids is illustrated by the formation of a 96% yield[350] of lauric acid from the reaction of dodecyl alcohol with platinum oxide and air, while many examples of the usefulness of hydrogen peroxide to effect similar conversions may be found in the review by Wallace[351].

Oxygen, alone and in the presence of a variety of catalysts, has been reported to effect conversion of alcohols to acids. At 100–180°C and in the presence of chloroacetic acid or some other strong acid, atmospheric oxygen has been used[352] to convert acetates of aliphatic alcohols to bifunctional aliphatic carboxylic acids, probably via the intermediate alcohols. In the presence of platinum on charcoal[353], sodium bicarbonate and water, pentaerythritol[354] and l-sorbase[355] have been converted by oxygen to trimethylolacetic and 2-keto-l-gulonic acid in 50% and 62% yields, respectively.

Cobalt(II) salts have also been found to be effective catalysts for the oxygen oxidation of glycols to diacids. Treatment of *trans*-1,2-dihydroxycyclohexane with oxygen in benzonitrile, at 100°C in the presence of cobalt(II) acetate, affords[356] adipic and succinic acids via the intermediate dialdehydes which may also be isolated. Under similar conditions 1,2-dihydroxy-*n*-decane is converted in 70% yield into pelargonic acid (equation 127)[356]. Esters[357] may also be produced during this reaction as shown by the oxidation of 1-hexanol in the presence of cobalt(II) acetate and cobalt(II) bromide in acetic acid which gives *n*-hexyl *n*-hexanoate.

$$C_8H_{17}CH(OH)CH_2OH \xrightarrow[CO(II)]{O_2,\ PhCN} C_8H_{17}COOH \qquad (127)$$

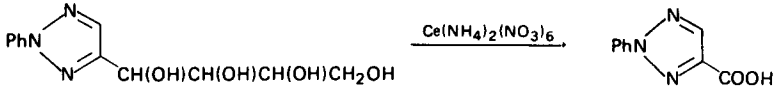
The use of catalytic quantities of Co(II) and Fe(III) have been found[358] to be necessary for the oxidation of phenol to *cis,cis*-muconic acid using peracetic acid, while the use of ammonium vanadate catalyses the oxidation of *p*-hydroxymethylbenzoic acid, *p*-(1-hydroxy-1-methylethyl)benzoic acid and *p*-di(1-hydroxy-

TABLE 3. Preparation of carboxylic acids from benzoins using ceric ammonium nitrate

Benzoin	Product	Yield (%)
Benzoin	Benzoic acid	86
4,4'-Dimethylbenzoin	4-Methylbenzoic acid	86
4,4'-Dimethoxybenzoin	Anisic acid	88
α-Naphthoin	1-Naphthoic acid	84
Furoin	2-Furoic acid	83

1-methylethyl)benzene, all to terephthalic acid[359] in the presence of aqueous hydrogen peroxide–hydrogen bromide mixtures.

i. With miscellaneous reagents. Although ceric ion normally oxidizes alcohols to aldehydes, special alcohols such as benzoins[360] are split into an aryl aldehyde and an aroyl radical upon treatment with ceric ammonium nitrate, and the radical formed is rapidly oxidized further to an arenecarboxylic acid (Table 3). Polyhydric alcohols, such as glucose phenylosotriazole, are also oxidized by ceric ion to acids, such as 2-phenyl-1,2,3-triazole-4-carboxylic acid (equation 128)[361].

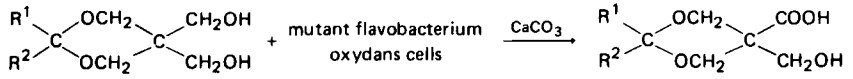


(128)

Three rather interesting reagents have been used to oxidize various alcohols to the corresponding carboxylic acids. Cold, alkaline triphenyltetrazolium chloride has been found[362] to effect an 80% conversion of Corterolone (Reichstein's compound S) to the hydroxy acid shown in equation (129), while xenic acid in water has been found[363] to be effective in oxidizing certain *vic*-diols and primary alcohols to their corresponding carboxylic acids.

(129)

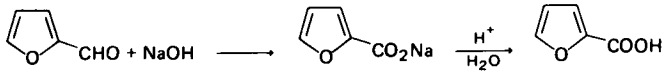
Mutant flavobacterium oxydans cells in the presence of calcium carbonate have been observed[364] to be an effective oxidizing agent for the conversion of disubstituted bis(hydroxymethyl)-1,3-dioxanes in 78–91% yields into disubstituted carboxyl hydroxymethyl-1,3-dioxanes (equation 130).



(130)

2. Oxidation of aldehydes

a. With base. The most common base-catalysed oxidation of aldehydes to carboxylic acids involves the reaction of aldehydes containing no α-hydrogen atoms with alkali, producing a primary alcohol and the salt of the corresponding acid. This reaction, known as the Cannizzaro reaction was reviewed[365] in 1944. One example is the conversion of furfural to 2-furoic acid in 60–63% yield (equation 131)[366]. Recently, the yield of this conversion has reportedly[367] been increased to 72–76%.



(131)

Passage of gaseous propanal, in a stream of nitrogen, over calcium hydroxide and zinc oxide at 450–470°C also gives rise to a Cannizzaro reaction[368] affording an 80% yield of pentan-3-one. This product is formed from condensation of the primary reaction products, propanol and propanoic acid, at these temperatures.

A modification of the Cannizzaro reaction discovered by Claisen[369] and later extended by Tishchenko[370] involves the use of sodium or aluminium alkoxides to convert both aliphatic and aromatic aldehydes into esters[371-374]. An example of this Tishchenko reaction is the conversion[375] of benzaldehyde in 90–93% yield to benzyl benzoate using sodium benzoxylate (equation 132). Nord and coworkers[376]

$$PhCHO + PhCH_2ONa \longrightarrow PhCOOCH_2Ph \qquad (132)$$

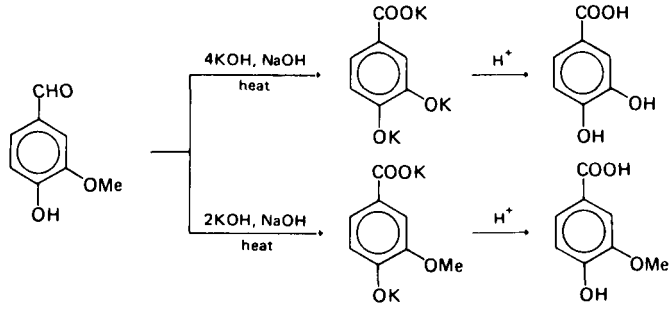
later investigated the use of magnesium aluminium complexes of the general formula $Mg[Al(OR)_4]_2$ as catalysts for this reaction, and found that in the presence of these reagents aldehydes of the type, RCH_2CHO, condense not only to afford simple esters, as with the sodium and aluminium alkoxides, but also to afford 'trimeric' esters (equation 133). In a still later study Villani and Nord[377],

$$RCH_2CHO + Mg[Al(OR)_4]_2 \longrightarrow RCH_2COOCH_2CH_2R + RCH_2CH(OH)CHRCH_2OOCCH_2R \qquad (133)$$

studied the use of various alkoxides with three aldehydes, butyraldehyde, octaldehyde and α-ethylbutyraldehyde. The yields of simple ester and glycol ester obtained for each of these aldehydes with each of the various metallic ethoxides used are recorded in Table 4. This study also revealed that aldehydes other than aliphatic ones having the α-CH_2 grouping do not afford appreciable yields of glycol esters with magnesium aluminium ethoxide and give zero yields of glycol esters with aluminium ethoxide. Stapp[378] has recently reported that boric acid but not *n*-butyl borate, acetic acid, or *p*-toluenesulphonic acid, could be used to effect a Tishchenko-type reaction as shown in equation (134). The reaction also failed when acrolein, furfural and crotonaldehyde were used.

$$RCHO + H_3BO_3 \xrightarrow[\text{cyclohexane}]{\text{heptane or}}{}_{250^\circ C} RCOOCH_2R \qquad (134)$$

Examples of base-catalysed conversions of aldehydes to carboxylic acids other than via the Cannizzaro and Tishchenko reaction also have been reported. Pearl has reported the conversion of vanillin to protocatechuic acid[379] in 89–99% yield and to vanillic acid[380] in 89–95% yield by caustic alkali fusion followed by acidification of the resulting potassium salts (equation 135). The base-catalysed



(135)

TABLE 4. Reaction of aldehydes with various metallic ethoxides

	Yields of simple esters and glycols (%) using					
	Butyraldehyde		Octaldehyde		α-Ethylbutyraldehyde	
Catalyst	Butyl butyrate	Monobutyrate of 2-ethyl-1,3-hexanediol[a]	Octyl octylate	Monooctylate of 2-hexyl-1,3-decanediol[a]	α-Ethylbutyl α-ethylbutyrate	Mono-α-ethyl butyrate of 2,2,4-triethyl-1,3-hexanediol[a]
$Al(OEt)_3$	81.6	0	69.1	0	70	0
$Mg[Al(OEt)_4]_2$	26.4	44.4	19.6	42.5	54	6
$Ca[Al(OEt)_4]_2$	14.6	22.9	12.0	20.5	–	–
$Na_2Mg(OEt)_4$	3.1	41.1	-	–	–	–
$Mg(OEt)_2$	7.1	32.1	3.2	28.0	-	–
$Ca(OEt)_2$	6.8	50.3	13.1	40.4	51	4.3
NaOEt	0[b]	0	0[c]	0	–	34.3

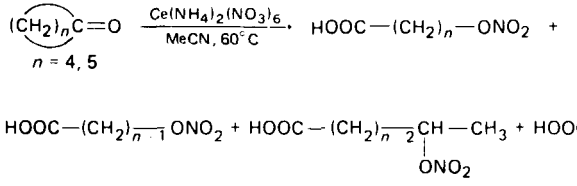
[a] The primary hydroxyl group of the diol is esterified.

[b] 88.5% of dehydrated aldol, α-ethyl-β-propylacrolein was obtained.

[c] 79.1% of dehydrated aldol, α-hexyl-β-heptylacrolein was obtained.

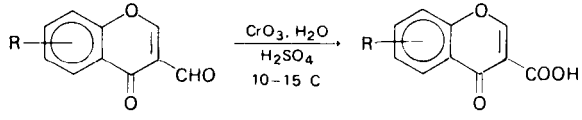
oxidation of 2-ethyl-1-hexanal to 2-ethyl-1-hexanoic acid has also been reported[381].

b. With ceric ion. The use of ceric ion for the oxidative conversion of aldehydes to the corresponding acids has been recently reviewed by Ho[382]. Using ceric ion, formaldehyde[383] and acetaldehyde[384] have been oxidized to formic acid, while cyclopentanone, cyclohexanone and norbornanone afford[385] nitrato carboxylic acids upon treatment with ceric ammonium nitrate in aqueous acetonitrile at 60°C (equation 136).



(136)

c. With oxides of chromium. Jones' reagent, chromium trioxide, water and sulphuric acid, has been the most widely used oxidizing mixture of chromium for the conversion of aldehydes to acids. It has been used to convert 2-adamantanal to 2-adamantanecarboxylic acid[386], and parent and disubstituted chromone-3-carboxaldehydes to their corresponding chrome-3-carboxylic acids, albeit in low yields (equation 137)[387]. Better yields were realized for the conversion of *cis*-4-octene-1,8-dialdehyde to *cis*-4-octene-1,8-dioic acid[388], which was converted to its methyl ester by reaction with diazomethane or methanol and sulphuric acid, and to its *t*-butyl ester by reaction with *t*-butyl alcohol and sulphuric acid (equation 138).



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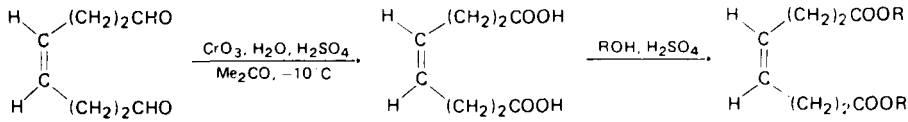

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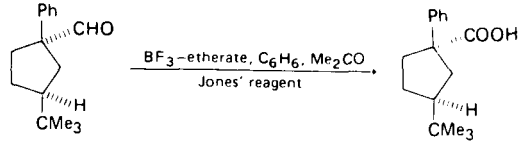
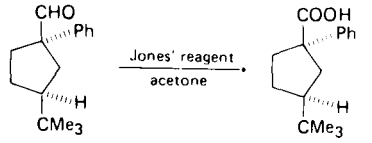


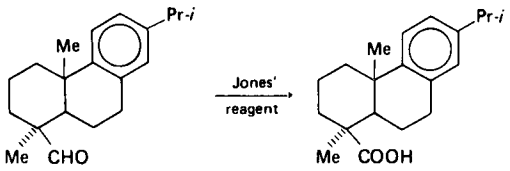
(139a)



(139b)

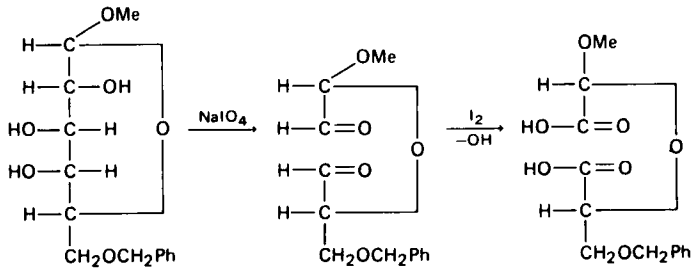
That the presence of double or triple bonds does not effect the course of reaction using Jones' reagent was demonstrated by the oxidation of *cis*-dec-2-ene-

4,6-diynal to *cis*-dec-2-ene-4,6-diynoic acid[389], while the retention of stereochemical configuration of substituents was demonstrated[390] by the conversion of 1-phenyl-*cis*- and *trans*-3-*t*-butylcyclopentanecarboxaldehyde to their corresponding 1-phenyl-*cis*- and *trans*-cyclopentanecarboxylic acids (equation 139). This stereochemical retention ability of Jones' reagent was utilized in the $C_{(4)}$ inversion of the diterpene resin acid dehydroabietic acid[391]. During the overall reaction sequence callitrisaldehyde was oxidized by Jones' reagent in 80% yield to (+)-callitrisic acid, thus allowing the inverted stereochemistry produced during the previous course of the reaction to be maintained.



(140)

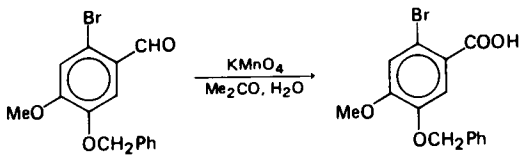
d. With periodic acid and periodates. Whereas sodium metaperiodate has been reported[392] to successfully convert 6-*O*-benzyl-α-D-galactopyranoside to its corresponding dicarboxylic acid, anomalous results have been observed[393] during the



(141)

periodic acid oxidation of several α,β-unsaturated carbonyl derivatives, reductones, to α-oxoglutaric acids.

e. With oxides of manganese. Examples of the use of potassium permanganate oxidation of aldehydes to carboxylic acids in water, aqueous acetone, pyridine, acid and basic solutions have all been reported. A 1% potassium permanganate solution in water at 90–95°C has been used[394] to convert 2,3,6-trichlorobenzaldehyde to 2,3,6-trichlorobenzoic acid in 24% yield, while a more concentrated solution of potassium permanganate in aqueous acetone has been used[395] to oxidize 5-benzyloxy-2-bromo-4-methoxybenzaldehyde to 5-benzyloxy-2-bromo-4-methoxybenzoic acid in 83% yield (equation 142). Pyridine solutions of potassium permanganate have been used[396] to oxidize side-chain aldehyde groups in steroids to carboxylic acids (equation 143).



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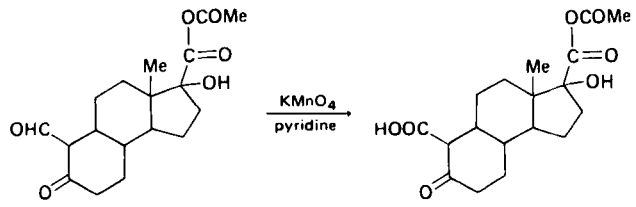
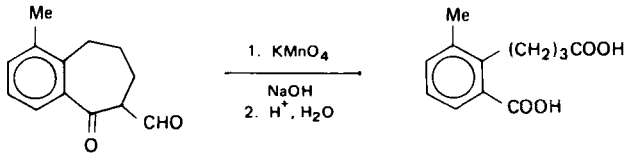


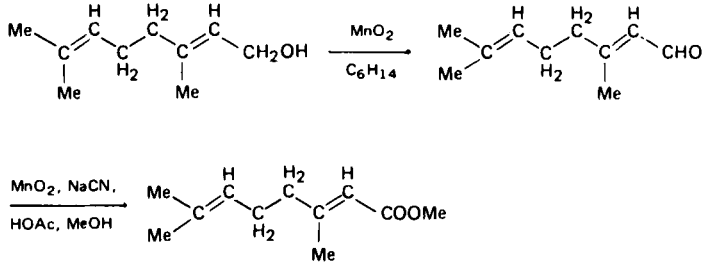
(143)

Treatment of heptanal with potassium permanganate in sulphuric acid affords[397] an 85–90% conversion to *n*-heptanoic acid while a 78–84% yield of piperonylic acid has been obtained[398] from piperonal upon treatment with alkaline potassium permanganate. Basic solutions of potassium permanganate have also been used to produce[399] γ-(2-carboxy-6-methylphenyl)butyric acid from 6-formyl-1-methylbenzosuber-5-one in 17% yield (equation 144), and 4′-fluorobiphenyl-3-carboxylic acid from 4-fluorobiphenyl-3-carboxaldehyde[400]



(144)

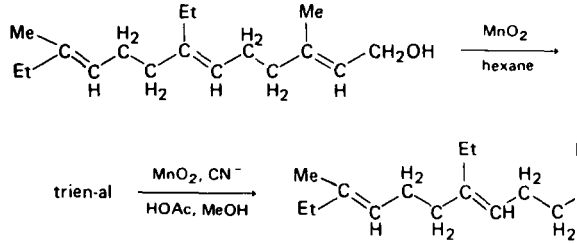
The most novel preparation of carboxylic acid esters from aldehydes using oxides of manganese is the method reported by Corey and coworkers[401]. This is a stereospecific method of converting α,β-unsaturated primary alcohols into carboxylic esters via their aldehydes. Firstly it involves the use of manganese dioxide in hexane to oxidize the alcohol to its aldehyde, and secondly the treatment of the aldehyde formed with manganese dioxide in the presence of cyanide ions in methanol to give, via suggested cyanohydrin and acyl cyanide intermediates, a conjugated carboxylic acid ester product. The conversion occurs in high yields and no *cis–trans* isomerization of the α,β-unsaturated double bonds is observed to occur. Corey[401] used this method to convert geraniol (*trans*-3,7-dimethyl-2,6-octadien-1-ol) via geranial into methyl geranate in 85–95% yield (equation 145). He also used this method[401] to convert farnesol, benzyl, cinnamyl and



(145)

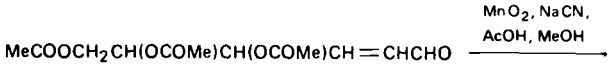
furfuryl alcohols into their methyl esters in 91–95% yield. This procedure has subsequently been successfully applied to a wide variety of alcohols and aldehydes for oxidation to their corresponding carboxylic acids. van Tamelen and McCormick[402] applied this procedure to the conversion of a *trans, trans, cis*-triene alcohol (a homologue of farnesol) into its methyl ester (used in the synthesis of a

juvenile hormone) (equation 146). Other conversions utilizing this procedure for the synthesis of *Cecropia* juvenile hormones have also been reported[403,404].



(146)

Corey's oxidation procedure has also been applied[405] to the conversion of biologically important aldehydes to their corresponding acids, and in the field of sugars to convert an unsaturated acetylated hexose[406,407] into its more unsaturated ester (equation 147). A mechanism for the conversion is proposed[406,407]. Other conversions which have been reported using this procedure are shown in equations (148)–(153).



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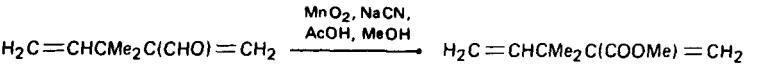

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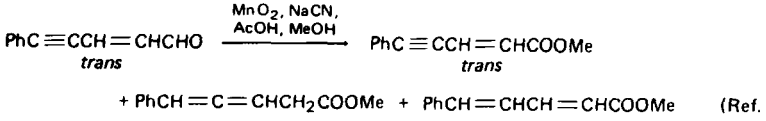

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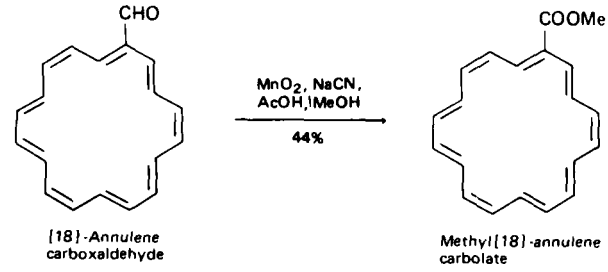

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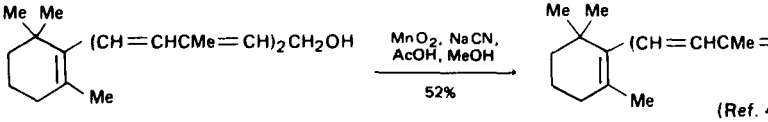


(151)

$$n\text{-}C_8H_{17}CH{=}C{=}CHCH{=}CHCHO \xrightarrow[65\%]{MnO_2,\ NaCN,\ AcOH,\ MeOH} n\text{-}C_8H_{17}CH{=}C{=}CHCH{=}CHCOOMe$$

trans *trans*

(Ref. 412) (152)

$$n\text{-}C_5H_{11}CH{=}CHCH{=}CHCHO \xrightarrow[92\%]{MnO_2,\ NaCN,\ AcOH,\ EtOH} n\text{-}C_5H_{11}CH{=}CHCH{=}CHCOOEt$$

trans, trans and *trans, cis* *trans, trans* and *trans, cis*

(Ref. 413) (153)

An extensive review of the use of *Active Manganese Dioxide in Organic Chemistry* has been published in two parts[414].

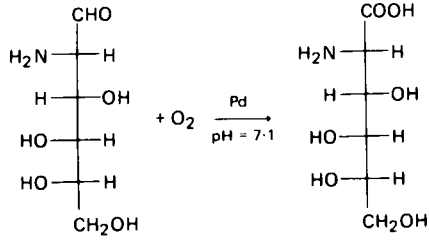
f. With oxides of nitrogen. Nitric acid in varying concentrations has been the reagent most widely used to oxidize aldehydes to carboxylic acids. 30% nitric acid at 95°C has been used[394] to oxidize 2,3,6-trichlorobenzaldehyde to 2,4,6-trichlorobenzoic acid, while 60% nitric acid under reflux for 16 hours was required[394] to oxidize 2,3,4-trichlorobenzaldehyde to 2,3,4-trichlorobenzoic acid. Fuming nitric acid was found[415] to effect a 60–65% conversion of β-chloropropionaldehyde, prepared from acrolein, to β-chloropropionic acid (equation 154).

$$CH_2{=}CHCHO \xrightarrow{HCl} ClCH_2CH_2CHO \xrightarrow{HNO_3} ClCH_2CH_2COOH \qquad (154)$$

g. With air, oxygen, acidified water and ozone. Treatment of C_4 and C_5 aldehydes in water with air at 25°C for 9 hours affords an excellent conversion[416] of the aldehydes to their corresponding acids (equation 155).

$$Me_2CHCHO + H_2O \xrightarrow[25°\,C]{air} Me_2CHCOOH \qquad (155)$$

In the presence of a variety of catalysts, oxygen has also been effective in converting various aldehydes to carboxylic acids. In the presence of a cuprous oxide–silver oxide catalyst, oxygen effected[417] an 86–90% conversion of furfural to 2-furoic acid, while in the presence of palladium at a pH of 7.1, oxygen effected[418] the conversion of an α-aminohexose into its corresponding α-amino acid in 54–60% yield (equation 156). Photochemically-induced oxygen oxidation



(156)

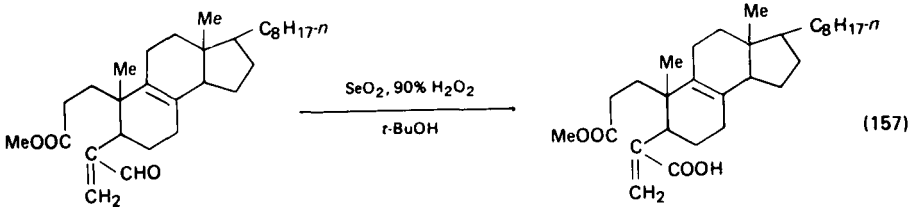
has been reported[419] to convert 19-oxo-5α-androstane-3β,17β-diacetate into its 19-carboxy derivative, when the irradiation was performed on an ethyl acetate solution of the aldehyde at 25°C for 0.5 hours.

An interesting preparation of levulinic acid in 45–69% yields involves the treatment of monomeric hexoses (4–5 h) or polymeric hexoses (6–8 h) with

hydrogen chloride–water azeotrope (20% hydrochloric acid) at 108°C and atmospheric pressure[420].

Ozone was found to be effective in oxidizing 6-formyl-1-methylbenzosuber-5-one to γ-(2-carboxy-6-methylphenyl)butyric acid, a conversion which was also accomplished with potassium permanganate (see Section II.G.2.e)[399].

h. With oxides of selenium. The use of selenium dioxide as an oxidizing agent has been reviewed[421], and a recent example[422] of its use in the field of triterpenes is shown in equation (157). In the presence of hydrogen peroxide in alcoholic media selenium dioxide has been used to oxidize acrolein to acrylates in 15–40% yield[423]. This method has also been used in the oxidation of other aldehydes in methanol or ethanol[424].



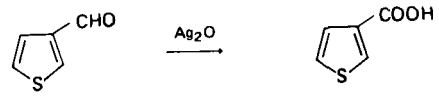
(157)

i. With oxides of silver. Several conversions of aldehydes to carboxylic acids previously reported in this review to have been accomplished with other reagents have also been reported, in most cases by the same authors, to have been effected with silver oxide. Corey and coworkers[401] reported the conversion of cinnamaldehyde, benzaldehyde and 3-cyclohexenylcarboxaldehyde to cinnamic acid (90%), benzoic acid and 3-cyclohexenylcarboxylic acid, respectively, upon treatment of the aldehydes with silver oxide and sodium or potassium cyanide in methanol. Corey also found[401] that a simple conversion of non-conjugated aldehydes to carboxylic acids could be effected by using silver oxide in tetrahydrofuran–water solutions (9:1) at 25°C under neutral conditions. Using this method and a molar ratio of silver oxide to aldehydes of 4:1, with a 14 hour reaction time, he was able to oxidize dodecanal and 3-cyclohexenylcarboxaldehyde to their corresponding acids in 90 and 97% yields, respectively. These results should be contrasted with the previous report in this review of the conversion of aldehydes to their corresponding acid esters upon cyanide-catalysed oxidation in methanol with manganese dioxide (Section II.G.2.e).

The report by Pearl[380], that vanillin was converted to vanillic acid by caustic alkali fusion also includes a prior report[425] of the same conversion being effected by silver oxide in 83–95% yield.

Conversion of callitrisaldehyde to (+)-callitrisic acid has also been accomplished[391] using silver oxide in methanol–water solution.

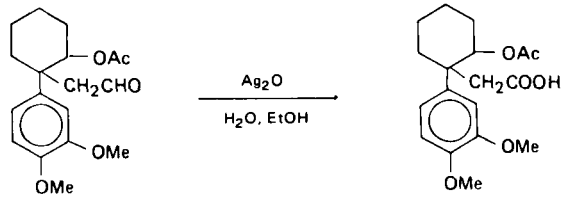
The uses of silver oxide to effect conversions of aldehydes to carboxylic acids which have not been previously reported to occur with other reagents are also reported in the literature. 5-Methylfurfuraldehyde upon treatment with silver oxide in methanol for 18 hours at 20°C affords[389] 5-methylfuroic acid, while *trans*-undec-3-ene-4,6-diynal upon treatment with silver oxide in methanol containing potassium hydroxide for 24 hours at 20°C affords[389] *trans*-dec-2-ene-4,6-diynoic acid. Two other examples of silver oxide oxidations of long-chain unsaturated aldehydes are the conversion of 6,10-dimethylundec-5,9-dienal in 55% yield[426] to its corresponding acid, and the liquid-phase oxidation, using added radical chain inhibitors, of α,β-unsaturated aldehydes[427] to their corresponding acids.



(158)

$$CH_3(CH_2)_4C{\equiv}CCH_2C{\equiv}C(CH_2)_7CHO \xrightarrow{Ag_2O} CH_3(CH_2)_4C{\equiv}CCH_2C{\equiv}C(CH_2)_7COOH \quad (159)$$

Silver oxide has been used as the oxidizing agent to convert 3-thenaldehyde to 3-thenoic acid in 95–97% yield (equation 158)[428], $\Delta^{9,12}$-stearadiynal to $\Delta^{9,12}$-stearadiynoic acid in 78% yield (equation 159)[429], *p*-tolualdehyde-α-D to *p*-toluic acid-α-D[430] and 2-acetoxy-1-(3,4-dimethoxyphenyl)cyclohexaneacetaldehyde to 2-acetoxy-1-(3,4-dimethoxyphenyl)cyclohexaneacetic acid (equation 160), an intermediate in the synthesis of (±)-mesembrine, in 93% yield[431].



(160)

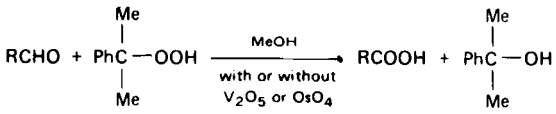
The electrolytic oxidation using silver oxide under neutral or mildly alkaline conditions previously reported[346] in this review (Section II.G.1.g) to effect good yields of carboxylic acids from alcohols has also been used to convert a variety of aldehydes to carboxylic acids as Table 5 indicates.

TABLE 5. Oxidation of aldehydes to carboxylic acids via electrolytic oxidation

Starting aldehydes	Acid product	Yield (%)
Benzaldehyde	Benzoic acid	51
Anisaldehyde	Anisic acid	57
Piperonaldehyde	Piperonylic acid	30
n-Hexaldehyde	*n*-Hexanoic acid	100
2-Ethylbutyraldehyde	2-Ethylbutyric acid	93
2-Ethylhexaldehyde	2-Ethylhexanoic acid	68
p-Nitrobenzaldehyde	*p*-Nitrobenzoic acid	38
Veratraldehyde	3,4-Dimethoxybenzoic acid	47

A comparative study of the oxidation of aldehydes to acids in aqueous base using silver oxide has been reported[432].

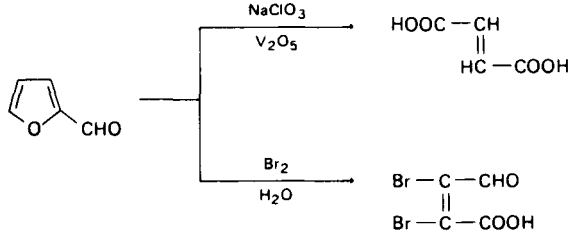
j. With miscellaneous reagents. Two metal oxides, other than those discussed thus far, which have been used to catalyse oxidation of aldehydes to carboxylic acids are osmium tetroxide and vanadium pentoxide. Both oxides have been separately used to catalyse the α,α-dimethylbenzyl hydroperoxide oxidation[433] of acetaldehyde, butyraldehyde, 2-ethylhexanal and benzaldehyde to their corresponding acids (equation 161). The oxidation has been found to occur with or without the oxides being present and the α,α-dimethylbenzyl hydroperoxide was found to be converted to 2-phenylpropan-2-ol during the reaction. Attempted oxidation of acraldehyde to acrylic acid was observed not to occur with or without



(161)

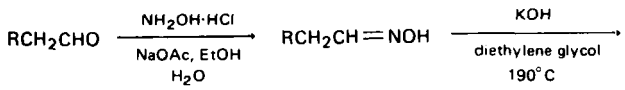
the oxides being present. *t*-Butyl hydroperoxide in the presence of metal salt catalysts, such as ferrous chloride and ferric chloride, has been used to oxidize methacrolein in methanol to methyl methacrylate[434].

Vanadium pentoxide was also found to be a useful catalyst in the sodium chlorate oxidative cleavage[435] of furfural to fumaric acid in 50–58% yield. Furfural also undergoes oxidative cleavage[436] with bromine water to give mucobromic acid (2,3-dibromo-3-formyl acrylic acid) in 75–83% yield (equation 162).



(162)

The conversion of aliphatic and aromatic aldehydes to aldoximes and their subsequent treatment with base in diethylene glycol at 170–190°C affords carboxylic acids (equation 163)[437,438]. This reaction which appears to proceed through the cyanide, which under the conditions used is then hydrolysed to the amide and finally to the acid, has been used[438] to prepare benzoic (95%), cinnamic (68%), enanthalic (63%), isobutyric (89%), phenylacetic (80%) and pivalic (38%) acids from their respective aldehydes. A reaction similar to this for the conversion of cinnamaldehyde to methyl hydrocinnamate, proceeding via its intermediate aminonitrile, has been reported[439].



(163)

An interesting reaction which demonstrates how the amount of silver ion present can effect the course of conversion of α-iodoheptanal to ethyl *n*-heptanoate has

TABLE 6. Preparation of carboxylic acids from aldehydes using Caro's acid

Aldehyde	Alcohol	Product	Yield (%)
Methacrolein	MeOH	Methyl methacrylate	90–94
Methacrolein	EtOH	Ethyl methacrylate	100
Methacrolein	*i*-PrOH	Isopropyl methacrylate	83
Acrolein	MeOH	Methyl acrylate	100
Crotonaldehyde	MeOH	Methyl crotonate	100
Propionaldehyde	MeOH	Methyl propionate	90
Benzaldehyde	MeOH	Methyl benzoate	100

TABLE 7. Preparation of carboxylic acids from aldehydes using silver(II) picolinate

Aldehyde	Acid
Butanal	Butyric acid
p-Tolualdehyde	*p*-Toluic acid
2-Ethylhexanal	2-Ethylhexanoic acid
2,3;5,6-Di-*O*-isopropylidene-α-D-mannofuranose	2,3;5,6-Di-*O*-isopropylidene mannoic acid
1,2;3,4-Di-*O*-isopropylidene-α-D-galactopyranose	1,2;3,4-Di-*O*-isopropylidene-α-D-galacturonic acid
2,3;4,5-Di-*O*-isopropylidene-D-fructopyranose	2,3;4,5-Di-*O*-isopropylidene-D-arabinohexulos-2-onic acid
2,3;4,6-Di-*O*-isopropylidene-L-sorbose	2,3;4,5-Di-*O*-isopropylidene-L-xylohexulos-2-onic acid
Benzaldehyde	Benzoic acid
2-Ethylbutanal	2-Ethylbutanoic acid
2-Furfuraldehyde	2-Furoic acid

been reported[440]. Treatment of α-iodoheptanal in ethanol–ether solution with a catalytic amount of silver ion affords ethyl *n*-heptanoate, while under the same condition with a stoichiometric amount of silver ion α-ethoxy-*n*-heptanal is the only product formed (equation 164).

$$C_5H_{11}CHICHO \xrightarrow[Ag^+\ (cat.)]{EtOH,\ ether} C_5H_{11}CH_2COOEt \qquad (164)$$
$$C_5H_{11}CHICHO \xrightarrow[Ag^+\ (stoichiom.)]{EtOH,\ ether} C_5H_{11}CH(OEt)CHO$$

Oxidation of aldehydes with Caro's acid (peroxymonosulphuric acid), prepared by treatment of sulphuric acid with hydrogen peroxide or from $(NH_4)_2S_2O_8$, in the presence of alcohols affords the corresponding acid esters in high yields[441] as Table 6 indicates. The mechanism proposed[441] for the reaction is shown in equation (165) and is suggested to proceed via a hemiacetal peroxymonosulphate.

$$R'CHO + R^2OH \xrightarrow{H^+} R'\underset{OH}{CHOR^2} \xrightarrow[-H_2O]{H_2SO_5} R'\underset{OOSO_2OH}{CHOR^2} \longrightarrow R'COOR^2 + H_2SO_4 \qquad (165)$$

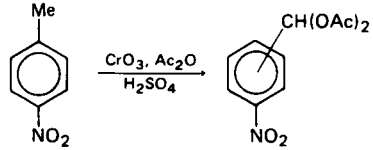
The most novel reagent which has been reported to effect oxidation of aldehydes is silver(II) picolinate[442]. Using this reagent in DMSO, a wide variety of alcohols and sugars have been effectively oxidized to their corresponding carboxylic acids as Table 7 indicates.

3. Oxidation of arenes

Since benzene di- and polycarboxylic acids, such as terephthalic acid, are of extensive industrial importance many of the reactions discussed in this section are oxidations of di- and polyalkylated benzenes which afford these acids.

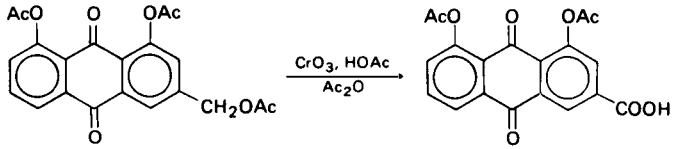
a. With oxides of chromium. Chromium trioxide in acetic acid–acetic anhydride–sulphuric acid mixtures has been used to oxidize alkyl groups on various

substituted benzenes to afford the corresponding carboxylic acid. Using this mixture of reagents, triphenyl(*p*-tolyl)silane was oxidized to *p*-(triphenylsilyl)benzoic acid[443] in 81% yield and 2-trichloroethyl-4-chlorotoluene was oxidized to 2-(β,β,β-trichloroethyl)-4-chlorobenzoic acid[444] in 93% yield, while *p*-nitrotoluene afforded a 65–66% *para* and 36–37% *ortho* mixture of nitrobenzaldiacetates (equation 166)[445].



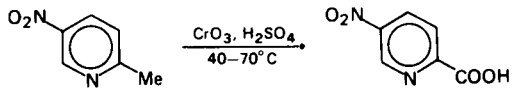
(166)

This reagent without the sulphuric acid, has been successfully applied to the oxidation of alkyl groups in more complicated systems such as steroids[446], and in aloe-emodin triacetate which was oxidized[447] to rhein diacetate (equation 167).



(167)

The use of chromium(VI) oxide in sulphuric acid as an oxidizing agent has also been successfully applied to alkyl side-chains of heterocyclic systems. Using this reagent mixture 3,4-dinitrotoluene was successfully[448] oxidized to 3,4-dinitrobenzoic acid, and 2-methyl-5-nitropyridine was oxidized to 5-nitropyridine-2-carboxylic acid in 80% yield (equation 168)[449].



(168)

Dichromate salts in water or sulphuric acid solutions have also found extensive use as oxidizing agents for arenes. Using sulphuric acid solution of sodium dichromate, *p*-nitrotoluene has been oxidized[450] to *p*-nitrobenzoic acid in 82–86% yield, 2,4,6-trinitrotoluene has been oxidized[451] to 2,4,6-trinitrobenzoic acid in 57–69% yield, and pentafluorobenzaldehyde has been oxidized[452] to pentafluorobenzoic acid in 75% yield (equation 169).

$$C_6F_5CHO \xrightarrow[\substack{H_2SO_4,\ 100^\circ C,\\ 2{\cdot}5\ h}]{Na_2Cr_2O_7,} C_6F_5COOH \qquad (169)$$

In water solutions sodium dichromate in an autoclave at 250°C has been used to oxidize 1,2-dimethylnaphthalene to 1,2-naphthalenedicarboxylic acid in 87–93% yield[453], and at 275°C has been used to oxidize ethyl benzene to phenylacetic acid[454]. The same mixture without the use of an autoclave has been used to oxidize acenaphthene and its chlorine, alkyl, hydroxyalkyl and sulphonic-acid substituted derivatives to the corresponding naphthalic acid derivatives[455], and 2-, 3-, 4-, 5- and 6-methylbenzo[c]phenanthrenes to their corresponding carboxy

compounds[456]. In acetic acid solution, 2-acetylfluorene has been oxidized using sodium dichromate to fluorene-2-carboxylic acid in 67–74% yield[457].

Heterocycles such as 3-picoline have been oxidized[458] to their corresponding nicotinic acids using neutral or alkaline solutions of sodium dichromate at 200–250°C.

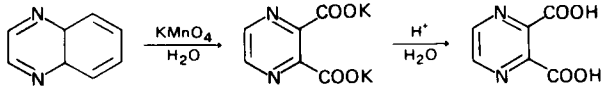
Oxidation of alkyl-substituted aromatic compounds using aqueous solutions of potassium dichromate and sodium nitrate have been reported[459] to produce the mono- and dicarboxylic acid salts of the aromatic starting material.

b. With periodic acid and periodates. Although the use of periodic acid and periodates as oxidizing agents in organic and bio-organic chemistry has been recently and thoroughly reviewed[325], one application of these reagents which should be mentioned is their use in oxidizing amines to carboxylic acids. Treatment of 3-phenyl-3-hydroxy-1-(diethylamino)propane with sodium periodate affords[460], via cleavage, 3-phenyl-3-hydroxypropanoic acid as one of the products (equation 170). Similar treatment[460] of 1-phenyl-2-piperidinoethane and 1-phenyl-2-morpholinoethane affords phenylacetic acid, also as one of their cleavage products.

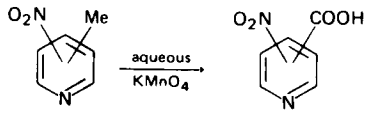
$$PhCH(OH)CH_2CH_2N(Et)_2 \xrightarrow{NaIO_4} PhCH(OH)CH_2COOH \qquad (170)$$

c. With oxides of manganese. The oxidation of arenes to carboxylic acids using potassium permanganate has been accomplished in a wide variety of solvents including water, aqueous base, acetic acid, acetone and crown ethers.

In water, potassium permanganate has been used to effect oxidation of *o*-chlorotoluene to *o*-chlorobenzoic acid in 76–78% yield[461] and quinoxaline to 2,3-pyrazinedicarboxylic acid in 75–77% yield (equation 171)[462]. Using this same mixture, α-picoline has been oxidized to picolinic acid[463], which was then treated with hydrogen chloride to produce picoline acid hydrochloride in 50–51% yield, while Brown[464,465] was able to obtain all the isomeric nitropyridine carboxylic acids from their corresponding nitropicolines (equation 172).



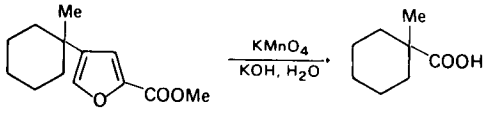
(171)



(172)

Position		Yield
NO_2	Me	(%)
3	2	45
4	2	51
5	2	30
6	2	45
2	3	42
4	3	45
5	3	40
6	3	52
2	4	37
3	4	35

In aqueous alkaline solutions, potassium permanganate has been used to oxidize methyl 4-(1-methyl-1-cyclohexyl)-2-furoate to 1-methylcyclohexanoic acid in 55% yield (equation 173)[466], *p*-tolylmercuric chloride to *p*-chloromercuribenzoic acid in 61–74% yield[467], napthalene to phthalonic acid which upon treatment with sodium bisulfide affords phthaldehydic acid in 40–41% yield (equation 174)[468],



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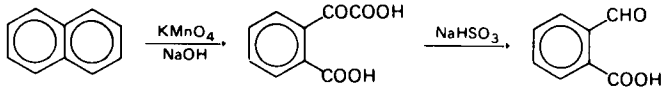
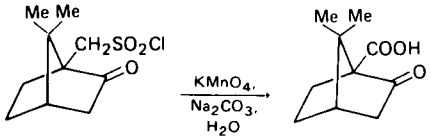


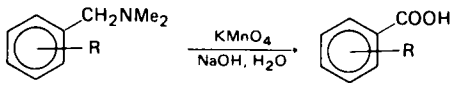
(174)

D,L-10-camphorsulphonyl chloride to D,L-ketopinic acid (2-oxo-1-apocamphanecarboxylic acid) in 38–43% yield (equation 175)[469], and 1,4-bisbromomethyl-2,3,5,6-tetrafluorobenzene to 2,3,5,6-tetrafluorophthalic acid[452].



(175)

Using sodium hydroxide solutions of potassium permanganate, Kantor and Hauser[470] converted 2,3-dimethylbenzyl alcohol and 2,3,4-trimethylbenzyl alcohol into 2,3-dimethylbenzoic acid and 2,3,4-trimethylbenzoic acid in 71 and 73% yields, respectively. With these oxidation results as models, this procedure was applied[470] to the oxidation of various substituted benzyldimethylamines to produce the corresponding substituted benzoic acids as shown in equation (176).



(176)

Starting material	Product	Yield (%)
2-Methylbenzyldimethylamine	*o*-Toluic acid	65
2,3-Dimethylbenzyldimethylamine	2,3-Dimethylbenzoic acid	75
2,3,4-Trimethylbenzyldimethylamine	2,3,4-Trimethylbenzoic acid	41
2,3,4,5-Tetramethylbenzyldimethylamine	2,3,4,5-Tetramethylbenzoic acid	37
2-Benzylbenzyldimethylamine	*o*-Benzylbenzoic acid	26

Yields of oxidized products are also reported. Application of this procedure to benzyl di(*n*-butyl)amine afforded only benzoic acid. If the amount of potassium permanganate used in the oxidation of 2,3-dimethyl-, 2,3,4-trimethyl- and 2-benzylbenzyldimethylamine was significantly increased over the amount used to obtain the products reported in the above table, then these compounds were converted[470] into 1,2,3-benzenetricarboxylic acid (hemimellitic acid), 1,2,3,4-benzenetetracarboxylic acid (prehnitic acid) and *o*-benzoylbenzoic acid in 75, 37 and 69% yields, respectively.

A kinetic study of the use of potassium permanganate in acetic acid to oxidize a variety of substituted aromatic compounds, such as toluene, ethylbenzene, *n*-propylbenzene, *i*-propylbenzene, nitrotoluene, chlorotoluene, toluic acid and the xylenes, to their corresponding carboxylic acids has been extensively investigated and reported in a series of papers by Cullis and Ladbury[471]. Although the products obtained were those expected, these studies do establish the dependence of the initial oxidation rate on the hydrogen-ion concentration, and also, that the greater part of the oxidation in these reactions is done by Mn(III) or associated ions and not by direct oxidation by the permanganate ion.

Using acetone solutions of dichromate, perfluorotetralin has been oxidized to octafluoroadipic acid[472], which was then allowed to react with aniline to form the dianilinium octafluoroadipate used as an intermediate in the preparation of di-(*S*-benzthiouranium)octafluoroadipate.

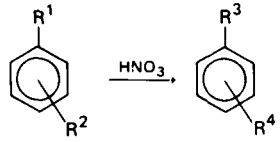
The most novel use of potassium permanganate as an oxidizing agent has been in crown ether solvents. Addition of these ethers to benzene allow up to 0.06 M of potassium permanganate to dissolve in the benzene producing the so-called 'purple benzene'. This material has been used[473] to effect the following conversions in the yields indicated; 1-heptanol to heptanoic acid (70%), benzyl alcohol to benzoic acid (100%), toluene to benzoic acid (78%) and *p*-xylene to toluic acid (100%). Another method of preparation of 'purple benzene', which affords this mixture more readily and does not require the use of the crown ethers, has been reported[474]. In this procedure quaternary ammonium ions are used to effect complete solution of the potassium permanganate in the benzene. This mixture has been used[474] to oxidize phenylacetonitrile and benzyl alcohol to benzoic acid in 86 and 92% yields, respectively, and also to oxidize 1-octanol to octanoic acid in 47% yield.

d. With oxides of nitrogen. The only oxide of nitrogen which has found extensive use in the conversion of arenes to carboxylic acids is nitric acid. In various concentrations and at various temperatures, nitric acid has been used to convert methyl, ethyl, propyl, *i*-propyl and even *t*-butyl substituents on aromatic or alicyclic rings to their corresponding carboxylic acids. In Table 8 are listed the dialkyl substituted benzenes which have been converted to their corresponding carboxylic acids using nitric acid in varying concentrations.

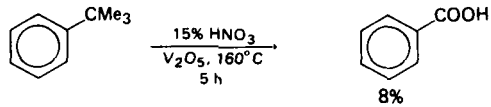
By using the results tabulated above Ferguson and Wims[478] developed a sequence for predicting the relative ease of oxidizing alkyl groups with nitric acid. They found that excluding the *t*-butyl group, the preferred oxidation of alkyl groups decreased in the order, *i*-propyl > ethyl > methyl, since this is the order of increasing electronegativity of the groups and also the order of increasing numbers of α-hydrogens. To further explore the selectivity they had proposed, they performed nitric acid oxidations on groups which have the same numbers of α-hydrogens but with varying electronegativities. Their findings showed that the relative ease of oxidation of alkyl groups, provided there is at least one α-hydrogen atom, is determined by the relative electronegativity of the alkyl group attached to the α-carbon atom. Thus, oxidation of *p*-isobutylethylbenzene afforded *p*-ethylbenzoic acid and *p*-*n*-propylethylbenzene afforded *p*-ethylbenzoic acid. Ferguson and Wims[478] further proposed that the above generalization concerning the relative ease of oxidation of carbon-attached side-chains only applied to hydrocarbon groups, and that once a carbon–oxygen, carbon–nitrogen or carbon–halogen bond was formed, the carbon attached to the ring was easily oxidized. To test this hypothesis they subjected *p*-methylbenzyl methyl ether to oxidation with 15% nitric acid and, as predicted, they obtained *p*-toluic acid as the only product.

Realizing the difficulty of oxidation of *t*-butyl substituents, Legge[480] attempted

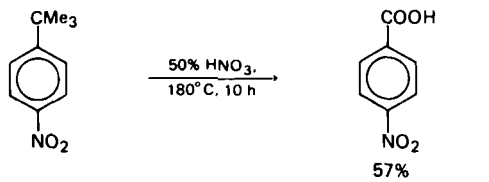
TABLE 8. Preparation of carboxylic acids from dialkylbenzenes using nitric acid



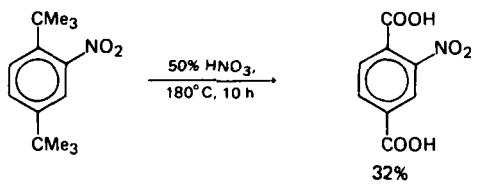
R^1	R^2	Conditions	R^3	R^4	Yield (%)	Reference
Me	*o*-Me	145–155°C, 55 h	Me	*o*-COOH	53–55	475
Me	*p*-$CHMe_2$	Reflux, 8 h	Me	*p*-COOH	51	476,478
Me	*p*-COMe	Reflux, 4 h	COOH	*p*-COOH	84–88	477
Me	*p*-Et	Reflux, 8 h	Me	*p*-COOH	–	478
Et	*p*-$CHMe_2$	Reflux, 8 h	Et	*p*-COOH	–	478
Et	*p*-(*t*-Bu)	Reflux, 8 h	*t*-Bu	*p*-COOH	–	478
$CHMe_2$	*p*-(*t*-Bu)	Reflux, 8 h	*t*-Bu	*p*-COOH	–	478
Et	*p*-(*n*-Pr)	Reflux, 8 h	Et	*p*-COOH	–	478
Et	*p*-(CH_2CHMe_2)	Reflux, 8 h	Et	*p*-COOH	–	478
Me	*p*-(*t*-Bu)	Reflux, 8 h	*t*-Bu	*p*-COOH	–	478
$CHMe_2$	*p*-(*t*-Bu)	Reflux, 11 h	*t*-Bu	*p*-COOH	66	479
$CHMe_2$	*m*-(*t*-Bu)	Reflux, 11 h	*t*-Bu	*m*-COOH	–	479
t-Bu	*p*-(*t*-Bu)	180°C, 9 h	COOH	*p*-COOH	30	480
Me	*p*-(CH_2OMe)	Reflux, 8 h	Me	*p*-COOH	–	478



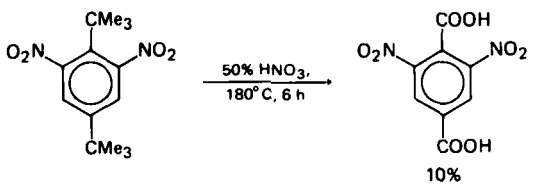
(177a)



(177b)



(177c)



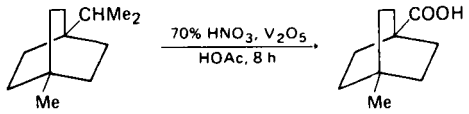
(177d)

the oxidation of *p*-di(*t*-butyl)benzene with chromium trioxide in acetic acid, aqueous potassium permanganate and 10–100% nitric acid under reflux and found that in all cases no reaction occurred. Finally, using 50% nitric acid at 180°C for nine hours he succeeded in oxidizing *p*-di(*t*-butyl)benzene to terephthalic acid in 30% yield. To establish if this procedure would be successful with more and less substituted *t*-butylbenzene derivatives he performed the reactions shown in equation (177).

Mono- and dicarboxylic acids are also obtained[481] by the acid decomposition of ω-nitrated arylnitroparaffins followed by nitric acid oxidation of the resulting aromatic monoacid. Using this procedure α-nitro-*p*-xylene was heated with concentrated hydrochloric acid in a glass pressure vessel for one hour at 150°C and afforded *p*-toluic acid which was subsequently oxidized to terephthalic acid in 96% yield by treatment with 30% nitric acid at 190°C for one hour.

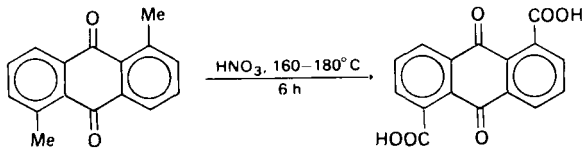
Alkylbenzenes containing multiple substituents have also been oxidized to the corresponding carboxylic acid. 4-Fluoro-2-nitrotoluene was oxidized to 4-fluoro-2-nitrobenzoic acid in 69% yield using 15% aqueous nitric acid at 190°C for five hours under pressure, while 2-bromo-4-nitrotoluene was oxidized to 2-bromo-4-nitrobenzoic acid in 76% yield[482] and 2,6-dibromo-4-nitrotoluene was oxidized to 2,6-dibromo-4-nitrobenzoic acid in 32% yield using aqueous nitric acid at 130–140°C in the presence of mercury[483].

Catalytic nitric acid oxidation has also been used to prepare bicyclic acids from bicycloalkanes. Thus, treatment of 1-isopropyl-4-methylbicyclo[2.2.2]octane with 70% nitric acid in acetic acid for eight hours in the presence of vanadium pentoxide affords[484] a 25% conversion to 4-methylbicyclo[2.2.2]octane-1-carboxylic acid (equation 178).



(178)

Nitric acid has also been used in the field of quinones to effect oxidation of 1,5-dimethylanthraquinone to anthraquinone 1,5-dicarboxylic acid in 93% yield (equation 179)[484]. This conversion was accomplished using concentrated nitric acid in a sealed tube at 160–180°C for six hours.



(179)

e. With sulphur compounds. Carboxylic acids and their derivatives can be obtained from the reaction of a variety of organic compounds with sulphur, water and a base, and with inorganic sulphates or sulphides. Sulphur, mixed with any one of a number of alkaline aqueous solutions to increase the solubility of the sulphur or the starting material in water, has been shown to be an extremely potent and selective oxidizing agent for the preparation of carboxylic acids from a variety of organic compounds as Table 9 indicates[485].

To initiate a study of the use of inorganic sulphates as oxidizing agents to effect carboxylic acid formation from a variety of products, Toland[486] investigated the

TABLE 9. Preparation of carboxylic acids using alkaline sulphur

Starting material	Base[a]	Acid product	Yield (%)[b]
m-Toluic acid	1.0 NaOH	Isophthalic	100.0
p-Toluic acid	1.0 NaOH	Terephthalic	100.0
m-Toluic acid	8.5 NaOH	Isophthalic	97.8
p-Toluic acid	8.5 NaOH	Terephthalic	97.8
p-Toluenesulphonic acid	1.0 NaOH	*p*-Sulphobenzoic +	38.5
		benzoic	29.0
m-Xylenesulphonic acid	1.0 NaOH	Isophthalic	63.6
p-Xylenesulphonic acid	1.0 NaOH	Terephthalic	46.2
Toluene	2.0 $CaCO_3$	Benzoic	61.0
m-Xylene	2.0 NaOH	Isophthalic	61.0
m-Xylene	1.3 Na_2CO_3	Isophthalic +	70.8
		benzoic	10.4
m-Xylene	2.0 $CaCO_3$	Isophthalic +	11.1
		m-toluic	12.0
m-Xylene	1.2 Na_2 IP[c]	Isophthalic	33.5
m-Xylene	10 NH_4OH	Isophthalic	87.2
m-Xylene	None	Isophthalic	29.0
p-Xylene	2.0 NaOH	Terephthalic	77.0
p-Xylene	1.1 Na_2S	Terephthalic	79.0
p-Xylene	2.4 Na_2CO_3	Terephthalic	86.0
p-Xylene	8.0 $Na_2B_4O_7$	Terephthalic	76.0
p-Xylene	10 NH_4OH	Terephthalic	96.2
Acetophenone	1.0 NaOH	Benzoic	28.0
1-Butanol	4.0 NaOH	Propionic + acetic	48.0
Furan	2.0 NH_4OH	Succinic	30.0
Thiophane	4.0 NH_4OH	Succinic	19.5
Propylene	1.1 KSH	Propionic +	12.5
		acetic	7.2
Acetone	1.3 NaOH	Acetic	4.5

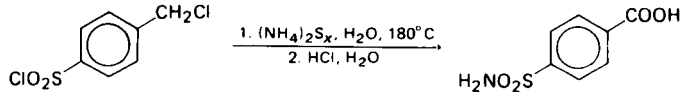
[a] Moles per mole of compound.
[b] Yields are based on the moles of stated product obtained and actual moles of starting material not recovered which could yield the product.
[c] Disodium isophthalate.

effectiveness of sulphur compounds of intermediate valences as oxidizing agents. His findings suggested that the presence of a lower valence state of sulphur was required to initiate the oxidation reaction.

To complete this study Toland then investigated the oxidative ability of various sulphates in the presence of various initiators. All the sulphates tried were found to be effective to varying degrees and the reader is referred to the original work[486] for more information. The sulphates used were: $(NH_4)_2SO_4$, $Al_2(SO_4)_3$, K_2SO_4, $KHSO_4$, $FeSO_4$ and Li_2SO_4. In a later study Toland[487] established that sulphur and water were effective in oxidizing the methylbenzenes to their respective carboxylic acids by heating the mixtures to 200–400°C under autogeneous pressures.

Inorganic sulphides have also been used to effect oxidation of aromatic alkyl side-chains to carboxylic acids. Treatment of *p*-toluic acid with sodium polysulphide, ammonium polysulphide or a sodium hydroxide–sulphur mixture affords terephthalic acid[488], while reaction of *p*-(α-chlorotoluene)sulphonic acid chloride

with ammonium polysulphide and water at 180°C for six hours affords a 48% conversion to benzoic acid sulphonamide (equation 180)[489].

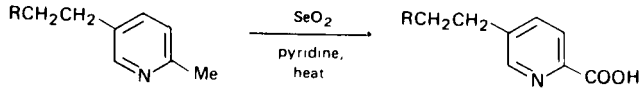


(180)

Dimerizations have also been reported during attempted oxidation of side-chain alkyl groups on aromatic molecules when sulphur compounds were used. Treatment of *m*- and *p*-toluic acids with sulphur affords the corresponding stilbenedicarboxylic acids[490], while treatment of *p*-toluic acid with several atmospheres pressure of hydrogen sulphide affords 4,4′-bibenzyldicarboxylic acid[491].

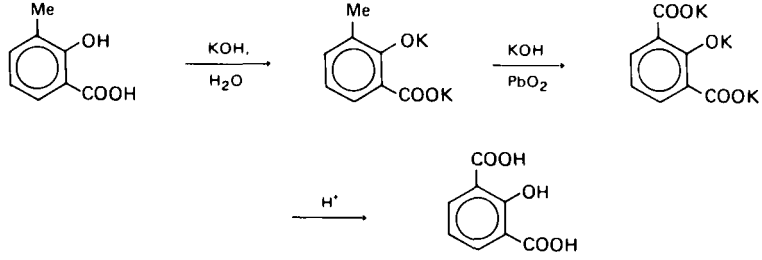
f. With oxides of selenium. Selenium dioxide alone or in combination with other reagents has been found to be moderately successful in oxidizing arenes and substituted arenes to their corresponding carboxylic acids. In the monoaromatic field, 2,3,5,6-tetrafluoroxylylene dibromide has been oxidized to 2,3,5,6-tetrafluoroterephthalic acid in modest yields using selenium dioxide[452]. In condensed ring systems 1,3,4,5,6,7,8-heptafluoro-2-methylnaphthalene was oxidized to 1,3,4,5,6,7,8-heptafluoro-2-naphthoic acid using selenium dioxide alone[472], while 2,6-dimethylnaphthalene was oxidized to 2,6-naphthalenedicarboxylic acid using selenium dioxide and nitrogen dioxide in water[492].

In the linear polyphenyl field 3-dibromomethyl-4′-fluorobiphenyl was oxidized to 4-fluorobiphenyl-3-carboxylic acid in 13% yield using selenium dioxide at 160–170°C for 10 minutes[400], while in the heterocyclic field 5-alkyl-2-picolines were oxidized to 5-alkylpyridine-2-carboxylic acids using selenium dioxide in boiling pyridine (equation 181)[493].



(181)

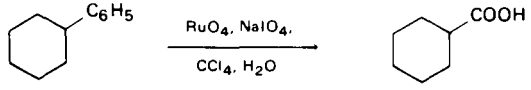
g. With other oxides of metals. Using a potassium hydroxide solution of lead dioxide, the dipotassium salt of 2-hydroxy-3-methylbenzoic acid can be oxidized to 2-hydroxyisophthalic acid in 46–61% yield (equation 182)[494].



(182)

Of the other oxides of metals used to oxidize arenes to carboxylic acids, ruthenium tetroxide has found the most extensive use. The ruthenium tetroxide used is conveniently prepared as a carbon tetrachloride solution by stirring ruthenium trichloride or ruthenium dioxide with a slight excess of sodium periodate and carbon tetrachloride overnight at room temperature. The presence of sodium periodate allows the ruthenium dioxide formed by the tetroxide substrate reaction

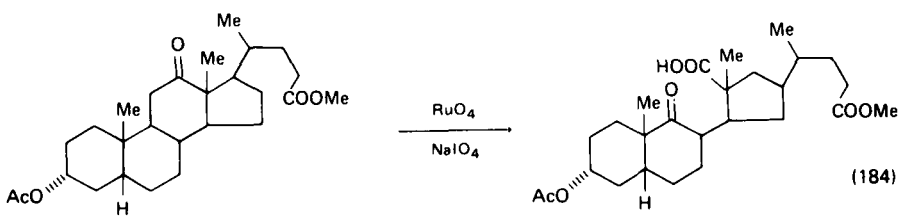
to be reoxidized to ruthenium tetroxide. Using this approach Caputo and Fuchs[495] were able to degrade benzene rings in a number of substrates, i.e. *cis*-2- and 3-phenylcyclobutanecarboxylic acids were oxidized individually to *cis*-1,2- and 1,3-cyclobutanedicarboxylic acid, identified as their dimethyl esters. Phenylcyclohexane, upon treatment with this reagent, was oxidized to cyclohexanecarboxylic acid (equation 183)[495], while *p*-(*t*-butyl)phenol was oxidized to pivalic acid.



(183)

In order to overcome the relative high cost and high molecular weight of the sodium metaperiodate which is the effective reagent in the above procedure, along with other drawbacks associated with the use of the above oxidation mixture, Wolfe and coworkers[496] developed a ruthenium trichloride-catalysed hypochlorite oxidation mixture. In this approach ruthenium tetroxide is still the actual oxidant, but household bleach, a readily available and inexpensive 5.25% aqueous solution of sodium hypochlorite, is the effective reagent. Preparation of the oxidation mixture[496] involves titration of a 2% aqueous ruthenium trichloride solution with 1.51 N sodium hypochlorite at 0°C until a yellow end-point is obtained. The resulting oxidation mixture is then added to a methylene chloride solution of the substrate and the mixture heated until a green-black colour develops. Using this approach, phenylcyclohexane was oxidized to cyclohexanecarboxylic acid in 25% yield in 10 days at 60°C, *p*-(*t*-butyl)phenol was oxidized to pivalic acid in 12% yield in seven days at room temperature, and the potassium salt of β-phenylpropionic acid was oxidized to succinic acid and benzoic acid in 95% and 6% yields, respectively, in three hours at room temperature.

The most effective use of ruthenium tetroxide as an oxidizing agent for arenes has been in the field of steroids. Examples of its effectiveness can be found in the reports of Caspi and coworkers[497], where using ruthenium tetroxide generated *in situ* from ruthenium dioxide and sodium periodate (with regeneration of the tetroxide from the dioxide formed using sodium periodate as above), oxidation of ring A or ring C of α,β-unsaturated steroids could be achieved. Thus, treatment with ruthenium tetroxide–sodium periodate mixtures oxidized testosterone to 17β-hydroxy-3,5-seco-4-nor-5-oxoanchostan-3-oic acid in 80% yield, 17β-acetoxy-3-oxo-3α-androst-1-ene to 17β-hydroxy-1,3-seco-2-nor-5α-androstane-1,3-dioic acid, 3β-acetoxy-5β-pregnan-16-en-20-one to 3β-hydroxy-17,20-dioxo-16,17-seco-5β-androstan-16-oic acid in 85% yield, and the ketone in equation (184) to methyl 3α-acetoxy-12-carboxy-9,12-seco-11-nor-9-oxo-5β-cholan-24-oate in 80% yield. Other significant oxidations are also reported[497].



(184)

h. With air, oxygen, peroxide and/or ozone. Very few oxidation reactions using oxygen as the oxidizing agent can be performed on a substrate without the

use of a catalyst. One such reaction is the oxidation of pentafluorobenzaldehyde to pentafluorobenzoic acid in 79% yield using a fine stream of oxygen bubbled through the aldehyde at 110°C for 20 hours[452].

A typical oxidation using oxygen, but employing a solvent-system catalyst, is the conversion of hexadecane in a propionic acid–acetic acid solution to a mixture of C_5 through C_{16} acids in 62% yield[498], using gases containing 14 volume % oxygen at 250 p.s.i. for five hours at 114–119°C.

Aqueous alkali solutions of oxygen have found extensive use as oxidizing agents for arenes, converting them to their corresponding carboxylic acids. Treatment of 1,6- or 2,6-dimethylnaphthalene with 7.5% sodium hydroxide aqueous solution at 260°C for one hour under oxygen pressure afforded naphthalenecarboxylic acid, phthalic acid and 1,2,4-benzenetricarboxylic acid[499], while treatment of 2,3-dimethylnaphthalene under the same conditions afforded the same three products reported above plus 1,2,4,5-benzenetetracarboxylic acid[499]. Aqueous alkali solutions of oxygen in the presence of catalysts have also been used to oxidize *o*-, *m*- and *p*-toluic acids into their corresponding dicarboxylic acids. In an expanded study Emerson and coworkers[500] found that a variety of catalysts could be used to oxidize *o*-, *m*- and *p*-toluic acids in a gas-agitated autoclave, at 260–275°C with aqueous sodium hydroxide and 1000 p.s.i. oxygen pressure for six hours. The catalysts used along with the yields obtained are shown in Table 10 for the oxidation of *p*-toluic acid to terephthalic acid. Emerson[500] also found that whereas the aluminium oxide component of the catalyst giving the highest yield could be replaced by oxides of zinc, cerium, titanium, zirconium or germanium with very little decrease in catalytic activity, replacement of the ferric oxide component with the oxides of cobalt, copper, manganese, nickel or lead afforded lower conversions. It was also found[500] that although air could be used in place of oxygen lower yields were obtained and similar lower yields were observed when potassium hydroxide–potassium carbonate was used in place of sodium hydroxide.

TABLE 10. Catalysts used for the oxidation of *p*-toluic acid to terephthalic acid, together with the yields obtained

Catalyst	Yield (%)
No catalyst	33
KVO_3	56–58
Fe_2O_3	55
$KMnO_4$	46
SeO_2	46
PbO_2	55
$K_2Cr_2O_7$	50
Fe_2O_3–Al_2O_3	66

Oxidation of the side-chains of alkyl or haloalkyl aromatics to aromatic acids was found[501] to be catalysed by a bromide in the form of hydrogen bromide[459], inorganic or organic bromides in the liquid phase with oxygen, air or hydrogen peroxide. Using this approach, *o*-, *m*- and *p*-toluic acids, *p*-hydroxybenzoic acid, *p*-xylene, *p*-diethylbenzene, *p*-nitrotoluene, *p*-methylbenzenesulphonic acid, γ-picoline, toluene, ethylbenzene, isopropylbenzene, cumic acid, α-hydroxycumic

TABLE 11. Oxidation of alkylbenzenes to carboxylic acids using cobalt(II) salts

Starting material	Catalyst	Acid product	Yield (%)	Reference
p-Xylene	$Co(OAc)_2 \cdot 4H_2O$ + HCl	Terephthalic	93	182
p-Toluic acid	$Co(OAc)_2 \cdot 4H_2O$ + HCl	Terephthalic	94	182
p-Xylene	$Co(OAc)_2 \cdot 4H_2O$ + NaBr	Terephthalic	94	182
p-*t*-Butyltoluene	$Co(OAc)_2 \cdot 4H_2O + NH_4Br$	*p*-*t*-Butylbenzoic	95	183
p-*t*-Butylbenzene	$Co(OAc)_2 \cdot 4H_2O$ + NaBr	*p*-*t*-Butylbenzoic	94	182
t-Butylbenzene	$Co(OAc)_2 \cdot 4H_2O$ + HCl	Benzoic	16	182
Alkylaromatics	Cobalt bromides	Alkylaromatic	25–70	184

acid, α,α,'-dihydroxydiisopropylbenzene *p*-diacetylbenzene, 2,6-dimethylnaphthalene, phenanthrene, mesitylene, *p*-cyanotoluene, acetophenone and α,α-dichloroxylene were all oxidized to their corresponding mono- or dicarboxylic acids using a variety of catalysts and conditions[501].

By far the most used catalyst for the oxygen-induced oxidation of alkylbenzenes has been the cobalt ion. In the form of its acetate, cobalt(III) acetate, it has been studied[502], along with manganese(III) acetate, as the catalyst in the oxygen oxidation of *p*-cymene affording *p*-isopropylbenzoic acid and *p*-acetobenzoic acid in 90 and 10% yields, respectively. Also in the form of its acetate, Co(III) was found[503] to effect a 91% conversion of *o*-bromotoluene to *o*-bromobenzoic acid, using an oxygen–hydrogen bromide–acetic acid mixture. The combination of cobalt(II) acetate and hydrochloric acid has also been shown[504] to be an effective catalyst for the oxidation of alkylbenzenes, providing a mixed solvent system consisting of chlorobenzene–acetic acid is used. Using this system yields of 92–94% were realized for the oxidation of *p*-xylene, *p*-toluic acid and *p*-*t*-butyltoluene as Table 11 indicates.

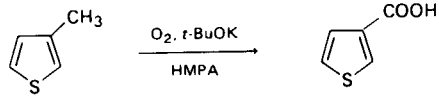
Air in the presence of a variety of catalysts has also been used[507] to oxidize arenes to carboxylic acids. Air has been used to oxidize *p*-*t*-butylbenzylbromide to *p*-*t*-butylbenzoic acid in the presence of copper nitrate[508], *p*-toluic acid to terephthalic acid in the presence of lead acetate[509] or cobalt naphthenate[510] and toluene or ethylbenzene to benzoic acid in the presence of alumina, alkaline-earth oxides, Fuller's earth or kieselguhr[511].

The autooxidation of side-chain alkyl groups to their corresponding carboxylic acids has received considerable attention since 1962. In dimethylsulphoxide-*t*-butyl alcohol–potassium butoxide mixtures, phenyl *p*-tolyl sulphone and methyl *p*-toluate have been reported[512] to undergo oxygen oxidation to phenyl *p*-carboxyphenyl sulphone and terephthalic acid, while *p*-ethyl- and *p*-isopropylbenzene, and *p*-nitro-, 2,4-dinitro- and 2,4,6-trinitrotoluene have been reported[513] to afford their corresponding carboxylic acids. In potassium *t*-butoxide–dimethylformamide solutions all three isomeric picolines have been oxidized[514] by oxygen to their corresponding carboxylic acids in the yields indicated: 2-picoline to picolinic acid in 59% yield, 3-picoline to nicotinic acid in 70% yield and 4-picoline to isonicotinic acid in 80% yield. Using potassium *t*-butoxide–diphenyl sulphoxide mixtures, toluene, *p*-nitrotoluene and *o*-xylene have been reported[515] to undergo oxygen oxidation to benzoic acid and a mixture of *o*-toluic and phthalic acid, respectively. Using potassium *t*-butoxide or potassium hydroxide in hexamethylphosphoramide, selective oxidation by oxygen of alkyl aromatics with varying side-chains to their corresponding aromatic carboxylic acid has been observed[516] to occur in the yields shown in Table 12. Employing this same system 2-methyl- and 2,5-dimethyl-

TABLE 12. Oxidation of alkylaromatics to carboxylic acids using potassium *t*-butoxide

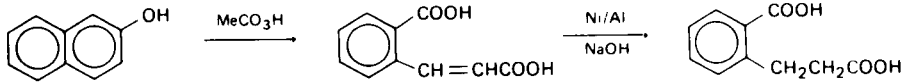
Reactant	Product acid	Yield (mole %)
Toluene	Benzoic	25–30
o-Xylene	Phthalic	35–40
m-Xylene	Isophthalic	50
p-Xylene	Terephthalic	15
Ethylbenzene	Benzoic	11
p-Cymene	*p*-Isopropylbenzoic	10
Tetralin	Phthalic	46

thiophene were converted to thiophene-2-carboxylic acid in 76 and 20% yields respectively[517], while 3-methylthiophene and toluene were oxidized to thiophene-3-carboxylic acid and benzoic acid in 19 and 50% yields respectively (equation 185).



(185)

Preparations of carboxylic acids have also been reported using peracids and hydrogen peroxide. In 40% peracetic acid β-naphthol was oxidatively cleaved to *o*-carboxycinnamic acid in 67–70% yield[518], which upon subsequent treatment with nickel–aluminium alloy (Raney catalyst) in sodium hydroxide afforded a 92–95% yield of β-(*o*-carboxyphenyl)propionic acid (*o*-carboxyhydrocinnamic acid) (equation 186). Hydrogen peroxide and heat have been found[519] to effect oxidation of the side-chain methyl group in the pyridine and quinoline palladium chloride complexes shown in equation (187) to produce the corresponding pyridine- and quinolinecarboxylic acid palladium chloride complexes, which upon treatment with acid afford the free acids. This reaction sequence has been performed on palladium chloride complexes made from 2-, 3- and 4-picoline and 2-, 3- and 4-methylquinoline.



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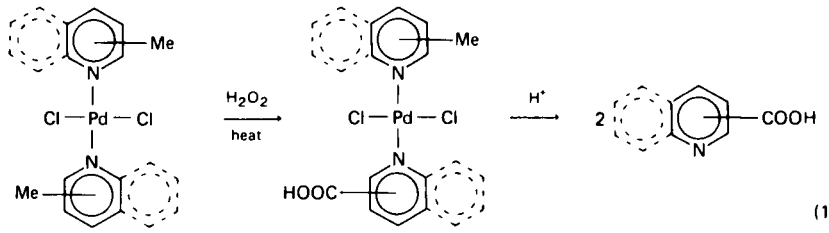
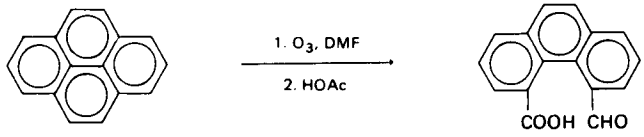


(187)

Ozone has also been found to be an effective reagent for the conversion of hydrocarbons into their corresponding carboxylic acids. In dimethylformamide, a

50% excess of ozone has been reported[520] to convert pyrene into 5-formyl-4-phenanthroic acid in 32–38% yield (equation 188). Using a mixture of ozone and air in ethyl acetate, *o*-isobornylphenol was converted[521] in 55% yield to racemic *exo*-camphane-2-carboxylic acid (equation 189), while under the same conditions,



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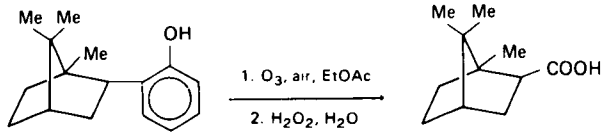
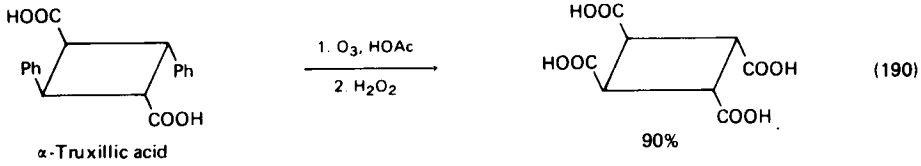


(189)

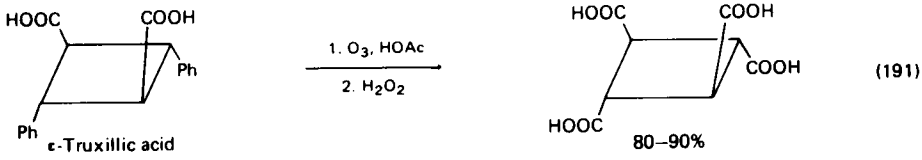
4-*exo*-isocamphenylguaiacol was converted to 2-*exo*-3,3-trimethylbicyclo[2.2.1]-heptane-6-*exo*-carboxylic acid. Application of a stream of ozone to an acetic acid solution of α-truxillic acid for 20 hours at room temperature affords a 90% conversion to 1,2,3,4-cyclobutane tetracarboxylic acid (equation 190)[522]. Similar results were obtained using ε-, γ- and *epi*-truxillic acids (equations 191 and 192), but *peri*-truxillic acid could not be oxidized under these conditions (equation 193).



α-Truxillic acid

90%

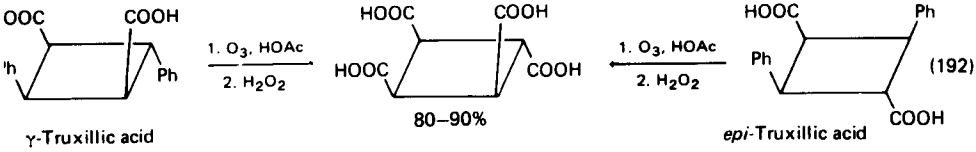
(190)



ε-Truxillic acid

80–90%

(191)



γ-Truxillic acid

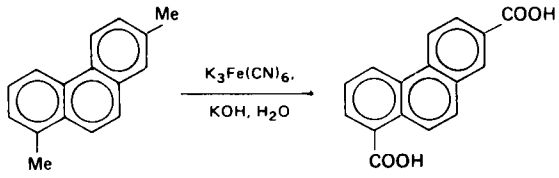
80–90%

epi-Truxillic acid

(192)

peri-Truxillic acid

(193)



(194)

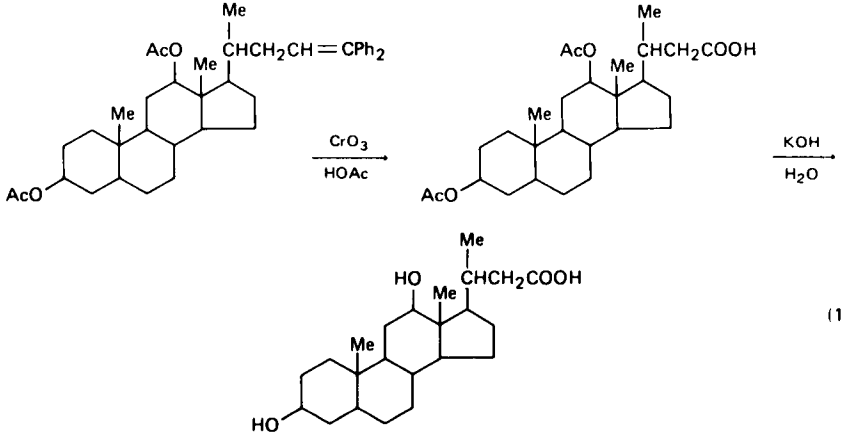
i. With miscellaneous reagents. An alkaline solution of potassium hexacyanoferrate(III) (potassium ferricyanide) has been reported[523] to successfully convert 1,7-dimethylphenanthrene to 1,7-phenanthrene dicarboxylic acid (equation 194).

4. Oxidation of double and triple bonds

a. With base. Reactions of multiple bonds with bases which give rise to carboxylic acids and/or esters are not well represented in the recent literature. However, one example of this mode of production of carboxylic acids is the formation[524] of butanoic acid from the reaction of isobutyl 2-hexenoate with potassium hydroxide at 300–340°C (equation 195).

$$MeCH_2CH_2CH{=}CHCOOCH_2CHMe_2 \xrightarrow[300-340^\circ C]{KOH} MeCH_2CH_2COOH \qquad (195)$$

b. With oxides of chromium. Chromium trioxide in acetic acid has been used[525] to prepare dec-9-ynoic acid and dec-9-enoic acid in 60 and 63% yields respectively, from 1,1-diphenylundec-1-en-10-yne and 1,1-diphenylundec-1,10-diene. This reaction illustrates the preferred cleavage by chromium trioxide of double bonds over triple bonds when both are present. Using the same oxidizing mixture, 3,12-diacetoxy-*bisnor*-cholanyldiphenylethylene has been cleaved[527] to 3,12-diacetoxy-*nor*-cholanic acid which was not isolated but was hydrolysed with 10% aqueous potassium hydroxide to 3,12-dihydroxy-*nor*-cholanic acid in 57–68% yield (equation 196). Potassium dichromate in sulphuric acid converts indene to homophthalic acid in 66–77% yield (equation 197)[530].



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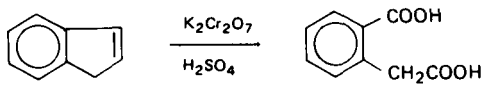
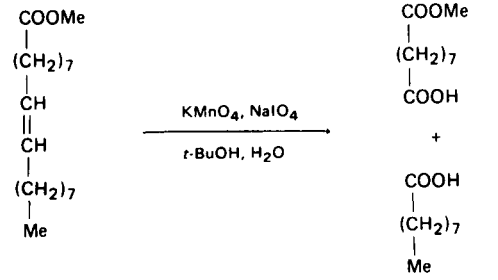


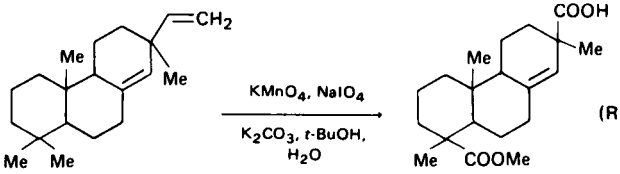
(197)

c. With Lemieux–von Rudloff reagent[325]. Although the oxidative cleavage of double bonds is not normally a useful method for obtaining carboxylic acids on a preparative scale, the use of the Lemieux–von Rudloff reagent[531-537] has proved very successful for this purpose. This mild reagent consists of aqueous sodium periodate and potassium permanganate at a pH of 7–8 and in a molar ratio of ~60:1. Studies[531-537] with this reagent have shown that the oxidation of an alkenic double bond by permanganate ion occurs via a π-complex and hypomanganate ester[308,309,538,539]. In the case of water-insoluble alkenes, good results were obtained when this oxidation mixture was used in aqueous *t*-butanol[534], pyridine[535,536] or *p*-dioxan solution[540]. The main advantages of this reagent have been found most useful in the analysis and structure determination of unsaturated fatty acids and their triglyceride derivatives (equation 198)[534,537,542-546], and in



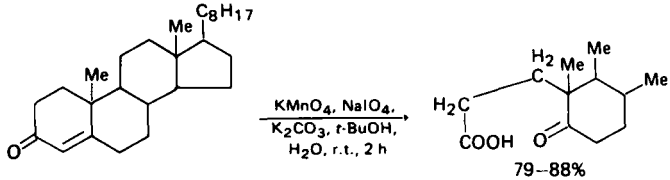
98–99% (Ref. 534) (198)

oxidative degradation of terpenes[532,533,536,547,548] and cyclic monoolefins[548,549]. The use of the permanganate–periodate reagent with monoene[550], diene and triene fatty acids[550] to optimize the oxidative cleavage has been described, as well as the non-quantitative oxidation of azelaic glycerides[551] and the unusual behaviour of some dienes (see equation 199)[552-555].



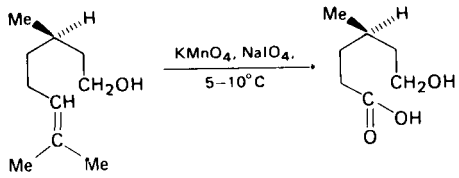
(Ref. 553) (199)

Oxidation of steroids[556] with potassium permanganate–periodate affords keto acids in excellent yields (equation 200). (*R*)-(+)-Citranello was oxidized[557] quanti-



(Ref. 556) (200)

tatively to (*R*)-(+)-6-hydroxy-4-methylhexanoic acid in an acetone–water medium (equation 201), while oxidation of a tricyclic α,β-unsaturated ketone to its corresponding keto acid was accomplished[558] in 80% yield and 15,16-dihydroxylinoleic



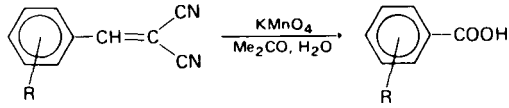
(201)

acid was oxidized to azelaic acid in good yield[559]. Evidence for the structure of the sex attractant of the gypsy moth was obtained by oxidation of (+)-10-acetoxy-*cis*-7-hexadecen-1-ol to 3-acetoxy-1-nonanoic acid in 92% yield and 7-hydroxy-1-heptylic acid, which was converted to pimelic acid in 71% yield upon treatment with alkaline permanganate (equation 202)[560]. The reagent attacked only the double bond, leaving the acetoxy and hydroxy groups unchanged.

$$\mathrm{Me(CH_2)_5CH(OAc)CH_2CH{=}CH(CH_2)_5CH_2OH} \xrightarrow{KMnO_4,\ NaIO_4} \mathrm{Me(CH_2)_5CH(OAc)CH_2COOH + HOCH_2(CH_2)_5COOH} \xrightarrow{KMnO_4} \mathrm{HOOC(CH_2)_5COOH} \quad (202)$$

Conversion of methyl propyl propynyl alcohol phosphate to DL-mevalonic acid 5-phosphate in 80% yield was accomplished[561,562] using the permanganate–periodate reagent, while lanosterol was oxidized to 3β-hydroxy-25,26,27-trisnorlanost-8-en-24-oic acid in 50% yield[563].

d. With oxides of manganese. Although manganese dioxide in acetic acid–acetic anhydride mixtures has been used[564] to oxidize 1-octene to a mixture of 3- and 4-decenoic acids, γ-decenolactone and 75% capric acid, and ethylene to a mixture of 20–25% γ-butyrolactone and 70–75% butyric acid, potassium permanganate is the oxide of manganese reagent of choice for oxidative cleavage of double bonds. In acetone solutions, potassium permanganate has been used to oxidatively cleave double bonds in steroids[565], and in benzalmalonitriles (equation 203)[566].



(203)

The α,β-unsaturated ester obtained from treatment of the methyl ester of mycoceranic acid (a mixture of the laevorotatory acid fraction from the lipids of tubercle bacilli) with pyridine has also been reported[567,568] to undergo double-bond cleavage upon treatment with potassium permanganate in acetone for six hours. Sodium permanganate in acetone has been reported to oxidize norbornene to *cis*-1,3-cyclopentanedicarboxylic acid in 75–95% yield[569].

Potassium permanganate in basic solutions has also been effective in producing carboxylic acids from double bonds. In aqueous acetone containing sodium bicar-

bonate, potassium permanaganate has converted 3,7-dimethyl-1-octene to 2,6-dimethylheptanoic acid in 45% yield[569], while in aqueous sodium hydroxide, potassium permanganate has converted 1-chloro-2,3,3-trifluorocyclobutene to 2,2-difluorosuccinic acid in 74–80% yield[570].

In aqueous acetone containing sulphuric acid, potassium permanganate has been used to oxidize a series of *N*-acylallylamines to *N*-acylamino acids[571], which upon acid hydrolysis afford *C*-perfluoroalkylglycines (equation 204).

$$C_nF_{2n+1}\underset{\underset{HNCOR}{|}}{CHCH{=}CH_2} \xrightarrow[Me_2CO,\ H_2SO_4,\ r.t.]{KMnO_4,} C_nF_{2n+1}\underset{\underset{HNCOR}{|}}{CHCOOH} \xrightarrow[H_2O]{H^+} C_nF_{2n+1}\underset{\underset{NH_2}{|}}{CHCOOH} \qquad (204)$$

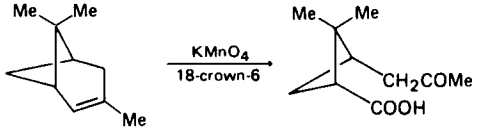
(19) (20)

n	R	% Yield 19	% Yield 20
1	$OCH_2C_6H_5$	85	57
1	C_6H_5	92	75
2	C_6H_5	82	62
3	C_6H_5	82	54

Permanganate ion in benzene and in the presence of a phase-transfer catalyst has been reported[572] to convert terminal olefins to carboxylic acids containing one carbon less than the starting material in excellent yields (equation 205). Using this same approach with the previously described 'purple benzene', α-pinene was converted in 90% yield to *cis*-pinoic acid (equation 206)[473], *trans*-stilbene in 100% yield to benzoic acid[473,474], cyclohexene in 100% yield to adipic acid[473] and 1-octene in 81% yield to heptanoic acid[474].

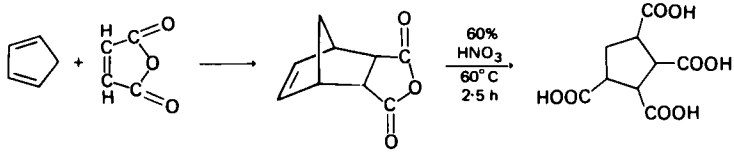
$$Me(CH_2)_5CH{=}CH_2 \xrightarrow[\substack{C_6H_6,\\ Q^+}]{MnO_4^-,} Me(CH_2)_5COOH \qquad (205)$$

Q^+ = phase-transfer catalyst



(206)

e. With oxides of nitrogen. Nitric acid (60%) has been used to oxidatively cleave[573] *endo-cis*-bicyclo[2.2.1]hep-5-ene-2,3-dicarboxylic anhydride, the adduct formed from reaction of cyclopentadiene with maleic anhydride, to *cis, cis cis*-1,2,3,4-cyclopentanetetracarboxylic acid in 80–85% yield (equation 207).



(207)

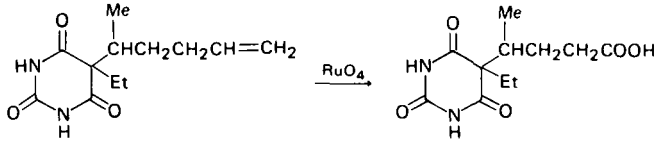
The most novel preparation of carboxylic acids and esters using an oxide of nitrogen has stemmed from the reaction of acetylenic hydrocarbons with nitrous

TABLE 13. Preparation of carboxylic acids via oxidation of acetylenes with nitrous oxide

Starting material	Conditions	Product	Yield (%)
Acetylene	EtOH, 300°C, 500 atm	Ethyl acetate	68
1-Hexyne	EtOH, 300°C, 500 atm	Ethyl hexanoate	56
1-Heptyne	MeOH, 250°C, 300 atm	Methyl heptanoate	57
1-Heptyne	MeOH, 300°C, 300 atm	Methyl heptanoate	87
Phenylacetylene	EtOH, 300°C, 500 atm	Ethyl phenylacetate	33
Phenylacetylene	H_2O, 300°C, 500 atm	Phenylacetic acid	20
5-Decyne	EtOH, 300°C, 500 atm	Ethyl 2-butylhexanoate	–
Diphenylacetylene	MeOH, 300°C, 500 atm	Methyl diphenylacetate	–

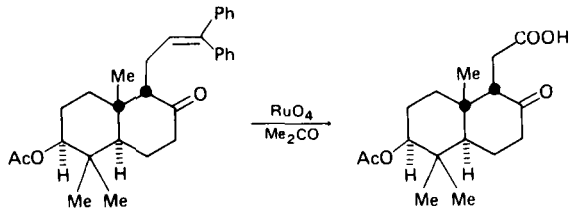
oxide at 200–300°C and 100–500 atm[574]. When this reaction is carried out in water carboxylic acids are formed, while using alcohols as solvents produces esters. The mechanism for this reaction is thought to involve initial formation of an α-diazo ketone or an α-diazo aldehyde which then loses nitrogen and undergoes anionotropic rearrangement to a ketene, which upon reaction with water or an alcohol leads to an acid or an ester. Listed in Table 13 are the acetylene starting materials and the conditions used, along with the products and yields obtained.

f. With oxides of ruthenium. Ruthenium tetroxide, prepared as previously described from the reaction of sodium metaperiodate with ruthenium chloride or ruthenium dioxide, has been used to oxidatively cleave cyclohexene to adipic acid in 86–95% yield[496], norborene to *cis*-1,3-cyclopentanedicarboxylic acid in 80–90% yield[575], and 5-ethyl-5-(1-methyl-4-pentenyl)barbituric acid to 5-ethyl-5-(1-methyl-3-carboxypropyl)barbituric acid in 81% yield (equation 208)[576].



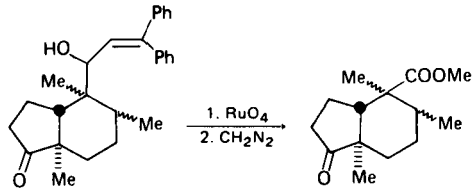
(208)

In the field of steroids, ruthenium tetroxide in aqueous acetone has been used to prepare[577] (–)-5,5-dimethyl-6-acetoxy-2-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydro-1-naphthaleneacetic acid in 89% yield from the diphenylethyleneacetoxyketone shown in equation (109). Comparable results were obtained with similar systems (equations 210 and 211)[578].



(209)

It has been reported[579] that when alkynes are treated with ruthenium tetroxide, prepared by reaction of ruthenium dioxide with sodium hypochlorite or sodium metaperiodate, in aqueous carbon tetrachloride at 0°C, a facile and rapid oxidation



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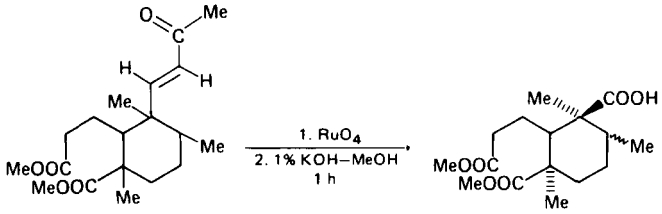


(211)

occurs converting the alkyne to its corresponding α-diketone and/or carboxylic acid. Table 14 reports the results obtained[579].

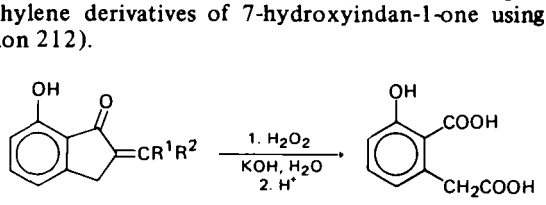
TABLE 14. Preparation of carboxylic acids via oxidation of acetylenes with ruthenium tetroxide

$$R^1C{\equiv}CR^2 \xrightarrow[CCl_4-H_2O,\ 0^\circ C]{RuO_4} R^1COCOR^2 + R^1COOH$$

Starting material	Diketone (mole %)	Acid (mole %)
$R^1 = R^2 = C_6H_5$	83.0	7.5
$R^1 = R^2 = Bu$	70.0	19.4
$R^1 = R^2 = Pr$	58.5	40.0
$R^1 = C_6H_5$, $R^2 = H$	–	66.0
$R^1 = t$-Bu, $R^2 = H$	–	60.0

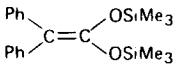
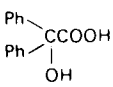
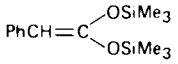
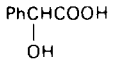
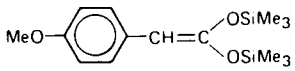
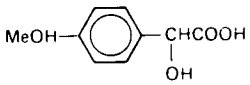
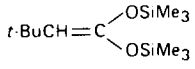
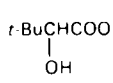
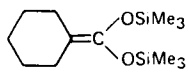
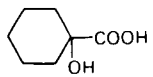
Although α-diketones can be cleaved with hypochlorite or periodate alone, under the conditions used in this investigation, all the diketones reacted too slowly to account for the amount of acid observed. It was also reported that no reaction occurred when hypochlorite alone was used[579].

g. With periodate, peroxyacids and ozone. The preparation of 3-hydroxyhomophthalic acid, a key precursor in the synthesis of 8-hydroxy-3(3′-hydroxy-4′-methoxyphenyl)dihydroisocoumarin (phylladulcin), has recently been reported[580] to have been accomplished by oxidative ring-cleavage of several substituted methylene derivatives of 7-hydroxyindan-1-one using basic hydrogen peroxide (equation 212).

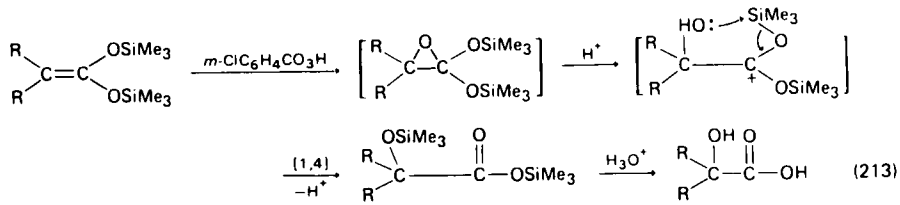


(212)

TABLE 15. Preparation of α-hydroxy carboxylic acids via oxidation of ketene bis(trimethylsilyl)acetals with *m*-chloroperbenzoic acid

Acetal	Product	Yield (%)
		81
		82
		83
		50
		80

An extremely general high-yield method for the preparation of α-hydroxy carboxylic acids has recently been reported[581] which involves oxidation of ketene bis(trimethylsilyl)acetals with *m*-chloroperbenzoic acid. The utility of this reaction is indicated in Table 15 which lists the starting acetals used and the products and yields obtained. The mechanism proposed[581] for this reaction is shown in equation (213), and involves initial preparation of an epoxide followed by ring-opening and a [1,4]-sigmatropic trimethylsilyl shift.



(213)

Although it had been previously reported that perbenzoic acid oxidation of phenylacetylene afforded phenylacetic acid[582], and that peracetic acid had no

effect on phenylacetylene[583], in a recent study[584] of peracid oxidation of phenyl- and diphenylacetylene with a methylene chloride solution of trifluoroperacetic acid containing disodium hydrogen phosphate afforded a 76% yield of benzil and a 17% yield of benzoic acid. Using the same reaction mixture with phenylacetylene afforded a 25% yield of benzoic acid and a 38% yield of phenylacetic acid, while with perbenzoic acid methyl phenylacetate (42.5%), ethyl phenylacetate (8.1%), methyl benzoate (3%), benzaldehyde (11.1%) and benzoic acid (43.5%) were obtained. Reaction of phenylacetylene with a methylene chloride solution of peracetic acid at room temperature afforded benzoic acid (23%) and phenylacetic acid (17%), but if the reaction was run using 40% peracetic acid in methylene chloride–acetic acid for 8 days a mixture consisting of 18% benzyl acetate, 39% acetylmandelic acid, 17% phenylacetic acid and 23% benzoic acid was obtained.

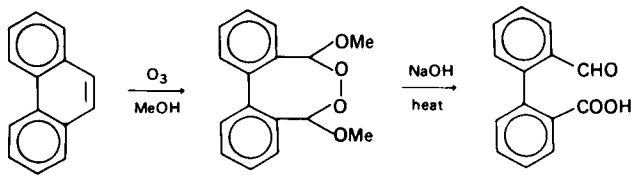
By far the premier reagent used to oxidize olefins to carboxylic acids has been ozone. At least five review articles have been published which discuss all or selected aspects of the ozonolysis reaction. In 1940 Long[585] reviewed 'The ozonization reaction', Bailey[586] in 1958 wrote on 'The reaction of ozone with organic compounds', in 1968 Murray[587] reviewed 'The mechanism of ozonolysis', Griesbaum[588] in 1969 discussed 'Carboxylic acid preparation by olefin ozonolysis', while in 1976 Dryuk[589] reviewed 'The mechanism of epoxidation of olefins by peracids'.

Ozonolysis of 2-hydroxymethylene-7-hydroxy-indan-1-one and 2-hydroxymethylene-7-phenylindan-1-one has been reported[590] to afford 3-hydroxyhomophthalic acid, while ozonolysis of norbornene affords[591-593] *cis*-1,3-cyclopentanedicarboxylic acid, both reactions occurring in good yields. On the other hand, a poor yield of only 3% was realized[594] in the preparation of 5-ethyl-5-(1-methyl-3-carboxypropyl)barbituric acid from 5-ethyl-5-(1-methyl-4-pentenyl)barbituric acid by ozonolysis.

Treatment of long-chain olefins with ozone has been reported under a variety of conditions and in the presence of a variety of catalysts. 1-Dodecene in pentane at $-10^{\circ}C$ and 1-tridecene in chloroform at $0^{\circ}C$ both afforded[595] their corresponding carboxylic acids, undecanoic and dodecanoic acid, respectively, upon treatment with ozone followed by hydrolysis. Using alcohols as solvents 1-dodecene was oxidized with ozone to undecanoic acid at -20 to $-30^{\circ}C$[596], while undec-10-ene-1-oic acid in ethanol was converted to 1,10-dodecanedioic acid in 50% yield using ozone[597].

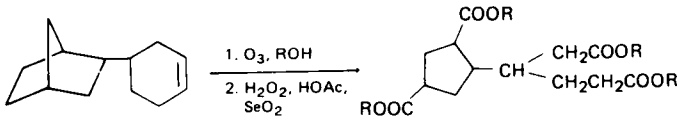
In 70% nitric acid at atmospheric pressure and in the presence of Ce(III) or Ce(IV) ions α- and β-olefins only are oxidized by ozone to carboxylic acids[598]. Branched-chain olefins are also oxidized[598] under these conditions if the branching occurs in other than the β-position for α-olefins or in the γ-position for β-olefins. Using acetic acid as the solvent stearolic acid has been oxidized by ozone to azelaic acid (1,9-nonanedioic acid) in 69–80% yield[599].

Ozone has also been used to ring-open cyclic molecules affording both mono- and dicarboxylic acids or esters. Treatment of phenanthrene with ozone in methanol affords[600] 3,8-dimethoxy-4,5,6,7-dibenzo-1,2-dioxocyclooctane which



(214)

upon sodium hydroxide hydrolysis gives diphenaldehydic acid (2′-formyl-2-biphenylcarboxylic acid) in 81–88% yield (equation 214). Ozonolysis of an ethyl bromide solution of 5-methyl-1-(2′,6′-dimethylheptyl)-1-cyclohexene or 1-dodecyl-5-methyl-1-cyclohexene followed by hydrogen peroxide–acetic acid hydrolysis of the ozonides affords 4,8,12-trimethyl-6-ketotridecanoic acid and 4-methyl-6-ketostearic acid in yields of 90% and 90–95%, respectively[569]. Reaction of cyclohexene, cyclohexenylnorbornene (equation 215), 3-methyl-4-(1-propenyl)-



(215)

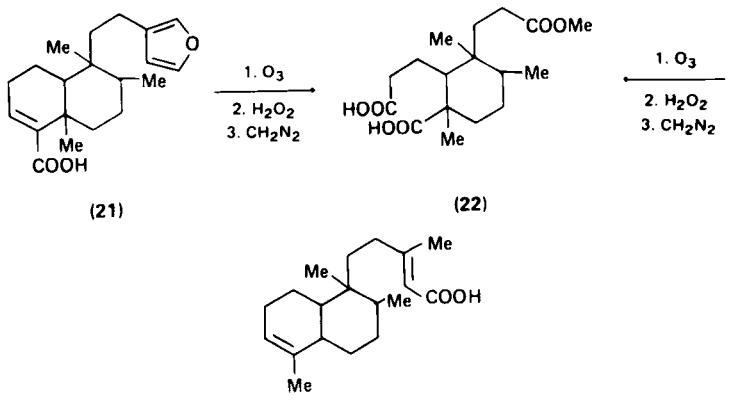
cyclohexene, 1-heptene and 4-vinylcyclohexene in methyl, *n*-butyl or *n*-octyl alcohols with ozone, followed by decomposition of the ozonides with hydrogen peroxide–acetic acid containing selenium dioxide, affords the corresponding ring-opened methyl, *n*-butyl or *n*-octyl esters in yields ranging from 35–70%[601]. Although the treatment of cyclic olefins with ozone followed by oxidation of the ozonides to the corresponding terminal diacid is the common[602-607] two-step process used by most workers for the oxidative cleavage of cyclic olefins, a novel one-step approach has been reported in which the initially formed ozonolysis products react immediately with the oxidizing reactant present. Thus, treatment[608,609] of olefins in emulsions of aqueous, alkaline hydrogen peroxide with ozone affords the α,ω-dicarboxylic acids listed in Table 16 in one step in the yields indicated. Reaction of cyclooctene in a hydrogen cyanide emulsion in water with ozone affords 2,9-dihydroxysebacic acid[609].

Ozone has also been used extensively in the field of terpenoids and steroids[610] to effect double-bond oxidative cleavage of carboxylic acids. Treatment of hardwickiic acid (**21**) (a constituent of the oleo-resin of *Hardwickia pinnata*) or kolavic acid (**23**) with ozone followed by hydrogen peroxide cleavage of the ozonide and esterification with diazomethane affords the methyl ester **22**[578]. Although it has been reported[611] that treatment of 3α-hydroxy-21-benzlidenepregnan-11,20-diene-

TABLE 16. Preparation of dicarboxylic acids via oxidation of olefin with hydrogen peroxide and ozone

Olefin	Carboxylic acid	Mole %
Cyclohexene	Adipic	26
Cyclooctene	Suberic	63
1,5-Cyclooctadiene	1,6-Dicarboxyhexene-3	52
1,5,9-Cyclododecatriene	1,10-Dicarboxydecadiene-3,7	60
Dicyclopentadiene[a]	2,3,5-Tricarboxycyclopentylacetic or	60
	6,8-dicarboxybicyclo[3.3.0]octene-4 and	
	1-carboxynorbornylene-2-acetic	55
Indene	Homophthalic	83
Acenaphthylene	1,8-Naphthalic	82
Norbornylene	Cyclopentanedicarboxylic-1,3	68
4-Cyclohexene-1,2-dicarboxylic anhydride	1,2,3,4-Tetracarboxybutane	73

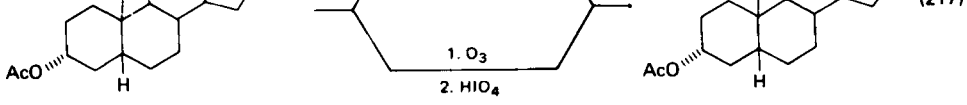
[a] Product depends upon conditions used.



(21) (22) (216)

(23)

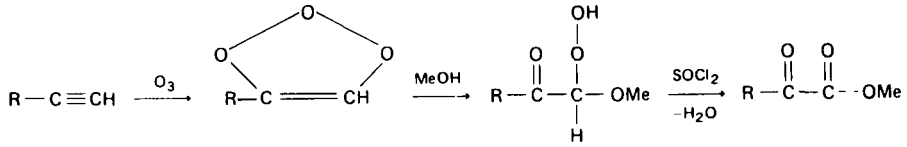
3-acetate (24) with ozone followed by periodic acid affords an 86% yield of 3α-acetoxy-11-ketoetianic acid (25), omission of the periodic acid treatment and reaction of 24 with excess ozone in ethyl acetate at −70°C, followed by treatment with zinc in acetic acid, gives the same product[612]. It was also reported[612] that ozonolysis of 3α-hydroxy-21-benzylidenepregnane-11,20-dione in ethyl acetate at −70°C followed by treatment with zinc in acetic acid affords 3,11-diketoetianic acid in 71% yield, while reaction of the dione with potassium permanganate in 85% aqueous acetone at room temperature for 15 hours affords a 62.8% yield of 3α-hydroxy-11-ketoetianic acid. In a similar manner a substituted carotenoid[613,614] was converted to 2,2-dimethylheptan-6-oneoic acid, and the acetate of 4,4a,4b,5,6,7,8,8a,9,10-decahydro-7-hydroxy-4b,8,8-trimethyl-2(3*H*)-phenanthrone was converted[579] to the acetate of 1,2,3,4,4a,5,6,7,8,8a-decahydro-6-hydroxy-2-oxo-5,5,8a-trimethyl-1-naphthalenpropionic acid.



(217)

(24) (25)

Reaction of ozone with triple bonds also leads to the production of carboxylic acids and esters regardless of where the triple bond is located in the molecule. Molecules containing interior triple bonds such as 5-decyne, upon treatment with ozone in carbon tetrachloride–acetic acid solutions give[615] a 35% yield of pentanoic acid, while ozone oxidation of diphenylacetylene has been reported[615,616] to yield 5–51% of benzil with the other product being benzoic acid. Ozonolysis of interior or terminal triple bonds produces acids, while the same reaction performed in alcohol solvents affords esters[617]. A novel preparation of α-keto methyl esters has been reported[618] to occur upon treatment of 1-hexyne, 1-octyne and phenyl-

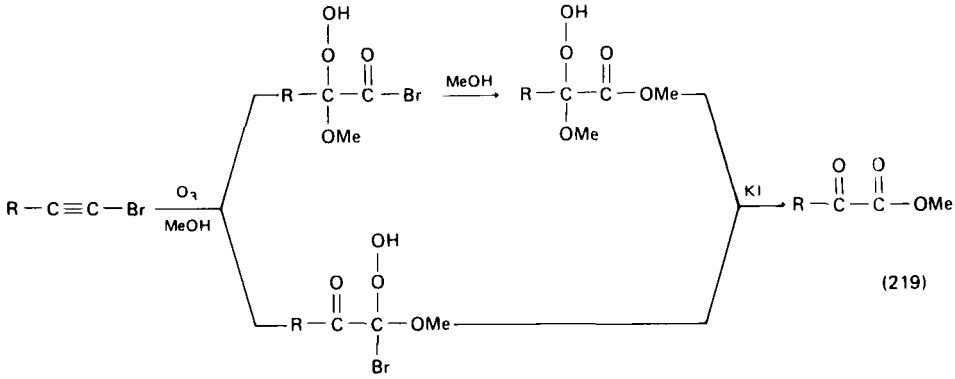


$R = C_4H_9, C_6H_{13}, C_6H_5$ (218)

acetylene with ozone in dry methanol, followed by dehydration of the intermediate α-hydroperoxy-α-methoxy aldehydes with thionyl chloride, as shown in equation (218). Unfortunately, this method gave the α-keto methyl esters in only 10- 20% yields. However, modification of the above reaction by using 1-bromoacetylenes, which are readily available from the corresponding terminal acetylenes by treatment with alkaline aqueous solutions of sodium or potassium hypobromite[619], gave the desired α-keto methyl esters shown in Table 17 via the mechanism shown in equation (219), in the yields indicated. Ozonolysis of the 1-bromoacetylenes in methanol solution should give two peroxides both of which can be converted to α-keto esters by reduction with potassium iodide.

TABLE 17. Oxidation of 1-bromoacetylenes with alkaline sodium or potassium hypobromite

Starting material	α-Keto ester	Yield (%)
$C_4H_9C{\equiv}CBr$	$C_4H_9COCOOMe$	40
$C_6H_{13}C{\equiv}CBr$	$C_6H_{13}COCOOMe$	50
$C_6H_5C{\equiv}CBr$	$C_6H_5COCOOMe$	50



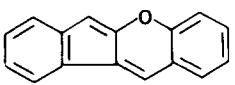
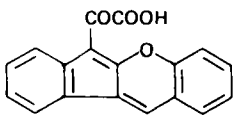
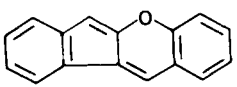
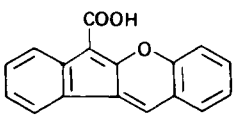
(219)

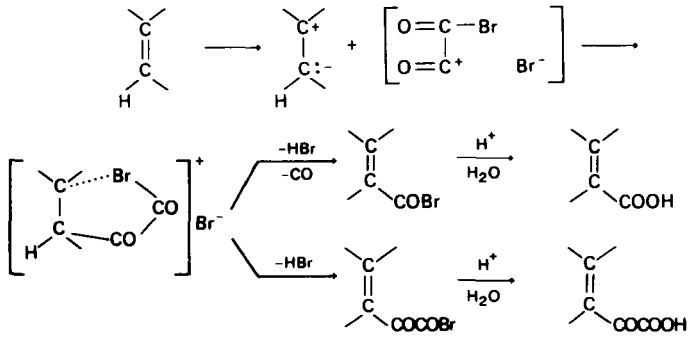
Carbohydrates containing terminal triple bonds have also been converted to carboxylic acids upon reaction with ozone in carbon tetrachloride solutions[620].

h. With miscellaneous reagents. Reaction of 11-hydroxy-10-oxoheptadecanoic acid with lead tetraacetate in 90% acetic acid for one hour affords heptanal and sebacic acid[525]. Other examples of the reaction of lead tetraacetate with triple bonds also appear in the literature[526-528].

A novel preparation[621a-d] of carboxylic acids involving the reaction of olefins with oxalyl chloride[621a-c] of oxalyl bromide[621d] has been used to prepare a

TABLE 18. Preparation of α,β-unsaturated acids via reaction of olefins with oxalyl bromide

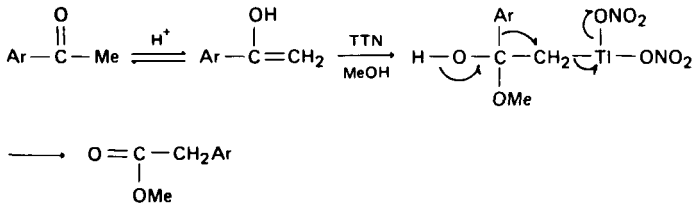
Starting material	Conditions	Carboxylic acid	Yield (%)
Isobutylene	CCl_4, 60°C, 15 h	β,β-Dimethylacrylic	12
Styrene	100°C, 4–5 h	Cinnamic	41
1,1-Diphenylethylene	Dioxane, 110°C, 6.5 h	β-Phenylcinnamic	52
Cyclohexene	110°C, 28 h	Cyclohexenecarboxylic	32
1-Methylcyclopentene	80–100°C, 3–4 h	1-Methylcyclopentenecarboxylic	29
Indene	90°C, 4–5 h	Indenecarboxylic	74
α-Pinene	Dioxane, 60°C, 6.5 h	α-Pinenecarboxylic	42
β-Pinene	Dioxane, 60°C, 6.5 h	β-Pinenecarboxylic	45
d,l-Camphene	CCl_4, 80°C, 5–6 h	Camphene-ω-carboxylic	57
α-Methylcamphene	Dioxane, 100°C, 5–6 h	α-Methylcamphene-ω-carboxylic	45
Anthracene	110–120°C, 8 h	Anthracene-9-carboxylic	52
Acenaphthene	CCl_4, 120–130°C, 18 h	Acenaphthene-5-carboxylic	50
Pyrene	80–90°C, 12 h	Pyrene-3-carboxylic	82
Anisol	100–105°C, 12 h	Anisic	55
α-Naphthol methyl ether	Dioxane, 60°C, 6.5 h	1-Methoxynaphthalene-4-carboxylic	83
β-Naphthol methyl ether	Dioxane, 90°C, 4.5 h	2-Methoxynaphthalene-1-carboxylic	42
	CCl_4, room temp., 4 days		46
	CCl_4, 70°C, 4 h		50



SCHEME 4.

wide variety of α,β-unsaturated acids in good yields. Although this reaction can be envisaged as leading to either α,β-unsaturated acids or α-keto-β,γ-unsaturated acids, the vast majority of olefins tried have produced only α,β-unsaturated acids. The mechanism for this reaction is shown in Scheme 4 and a tabular presentation of the results is given in Table 18.

The most utilitarian reagent to be recently used in the production of carboxylic acids and esters from enolates and acetylenes is thallium(III) nitrate (TTN)[622]. Unlike the Willgerodt–Kindler reaction[623-625] which transforms readily accessible alkyl aryl ketones into ω-arylakanoic acid derivatives, but suffers from the severe limitations of the high temperatures and pressures needed, the tedious and complicated isolation technique and poor yields of product, the use of TTN converts[626] acetophenones in one step into methyl phenyl acetates and avoids the above limitations. The mechanism[626] of this transformation is shown in equation (220)



(220)

and involves acid-catalysed enolization of the acetophenone, followed by oxythallation to produce an unstable alkylthallium dinitrate. Decomposition of this intermediate then proceeds via migration of the aryl substituent, resulting in direct formation of the methyl arylacetate and simultaneous reduction of thallium(III) to thallium(I). The substituted acetophenones used in this reaction are listed in Table 19 along with the yields of the corresponding methyl phenylacetates obtained.

Extension of this approach to the oxidation of acetylenes with TTN has also been reported[627,628]. Studies of this reaction with a variety of acetylenes indicates that the nature of the products obtained depends upon the solvent employed and the structure of the acetylene. Diarylacetylenes are converted into benzils in high yields upon treatment with TTN in either aqueous acidic glyme or in methanol, while dialkylacetylenes afford acyloins in aqueous media and -methoxy ketones in methanol. Monoalkylacetylenes on the other hand, undergo degradation

TABLE 19. Oxidation of acetophenones using thallium(III) nitrate

Starting product	Product	Yield (%)
C_6H_5COMe	$C_6H_5CH_2COOMe$	84
p-FC_6H_4COMe	p-$FC_6H_4CH_2COOMe$	44
p-MeC_6H_4COMe	p-$MeC_6H_4CH_2COOMe$	86
o-$MeOC_6H_4COMe$	o-$MeOC_6H_4CH_2COOMe$	62
3,4-$(MeO)_2C_6H_3COMe$	3,4-$(MeO)_2C_6H_3CH_2COOMe$	88
3-NO_2-4-$MeOC_6H_3COMe$	3-NO_2-4-$MeOC_6H_3CH_2COOMe$	61
p-HOC_6H_4COMe	p-$HOC_6H_4CH_2COOH$[a]	64
p-$C_6H_5CONHC_6H_4COMe$	p-$C_6H_5CONHC_6H_4CH_2COOMe$	66
2-$C_{10}H_7COMe$	2-$C_{10}H_7CH_2COOMe$	94

[a] Obtained by hydrolysis of the crude ester product.

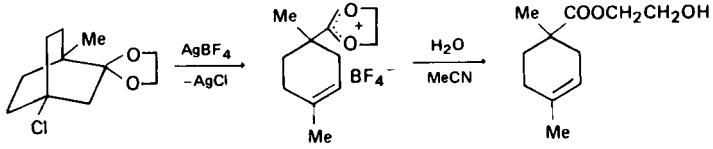
to carboxylic acids containing one carbon atom less than the starting material, while alkylarylacetylenes undergo a smooth oxidative rearrangement in methanol solution to give methyl α-alkylarylacetates. The acetylenes employed[627,628] which gave rise to acids or esters are shown in Table 20 along with the products and yields obtained.

TABLE 20. Oxidation of acetylenes using thallium(III) nitrate

Acetylenes	Products	Isolated Yield, %
$C_6H_{13}C{\equiv}CH$	$C_6H_{13}COOH$	80
$PhC{\equiv}CH$	$PhCH_2COOMe$	17
p-$O_2NC_6H_4C{\equiv}CH$	p-$O_2NC_6H_4CH_2COOMe$	0
p-$MeOC_6H_4C{\equiv}CH$	p-$MeOC_6H_4CH_2COOMe$	61
$PhC{\equiv}CMe$	$PhCHMeCOOMe$	80
$PhC{\equiv}CEt$	$PhCHEtCOOMe$	82
$PhC{\equiv}C(C_3H_7$-$n)$	$PhCH(Pr$-$n)COOMe$	83
$PhC{\equiv}C(C_4H_9$-$n)$	$PhCH(Bu$-$n)COOMe$	77
$PhC{\equiv}CCH_2CH_2Cl$	$PhCH(CH_2CH_2Cl)COOMe$	75
$PhC{\equiv}CCH_2Ph$	$PhCH(CH_2Ph)COOMe$	83
$PhC{\equiv}CCH_2CH_2Ph$	$PhCH(CH_2CH_2Ph)COOMe$	65
$PhC{\equiv}CBr$	$PhCHBrCOOMe$	70

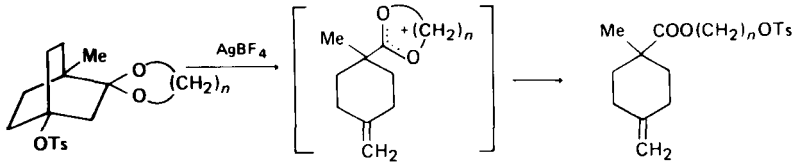
5. *Oxidation of ethers, acetals and ketals*

a. With boron fluorides. Reaction of the ethylene ketal of 1-methyl-4-chlorobicyclo[2.2.2]octan-2-one with silver tetrafluoroborate in absolute ether for 24 hours at room temperature affords[629] the corresponding dioxolonium tetrafluoroborate by silver-catalysed alkyl fragmentation of the ketal (equation 221). Hydro-



(221)

lysis of this salt in aqueous acetonitrile affords a glycol ester. Reaction of the corresponding tosylates leads to isomeric products (equation 222)[629]; however the intermediate salts cannot be isolated.



(222)

A mixture of boron trifluoride etherate and acetic anhydride at 0°C or below has been reported[630,631] to cleave a variety of steroidal methyl ethers. Allylic and homoallylic ethers were found to give their corresponding acetates in excellent yields, while completely saturated ethers gave the corresponding acetate with retention of configuration as the main substitution product, with the epimeric acetate and elimination products also being formed. Thus, using this procedure, cholesteryl methyl ether was converted to cholesteryl acetate in 93% yield, 4-cholesten-7β-ol methyl ether was converted to its acetate which was then hydrolysed to 4-cholesten-7β-ol, 4-cholesten-3β-ol methyl ether afforded 4-cholesten-3β-ol acetate and 3,5-cholestadiene, cholestanyl methyl ether was converted to cholestanyl acetate, cholestan-3α-ol methyl ether afforded cholestan-3α-ol acetate and lupanol methyl ether afforded only a 63% yield of A-nor-$\Delta^{3(5)}$-lupene.

b. With acids. Another interesting preparation of esters may be achieved[632] by the reaction of alkyl *t*-butyl ethers with carboxylic acids. This reaction, which proceeds in the presence of catalytic amounts of various proton-donating agents, e.g. sulphuric or *p*-toluenesulphonic acid, occurs according to equation (223), and has been found to give excellent yields in the cases shown in Table 21. A similar

$$R^1OBu\text{-}t + R^2COOH \xrightarrow{H^+} R^2COOR^1 + CH_2{=}CMe_2 + H_2O \qquad (223)$$

exchange[633] of allylic groups of ethers and esters with active hydrogen compounds has been found to be catalysed by any of the following mixtures: bis(triphenylphosphine)palladium chloride plus sodium phenoxide, palladium acetate plus triphenylphosphine, or zerovalent palladium complexes such as tetrakis(triphenylphosphine)palladium and (maleic anhydride)bis(triphenylphosphine)-

TABLE 21. Preparation of esters via reaction of alkyl *t*-butyl ethers with carboxylic acids

R^1	R^2	R^2COOR^1	Yield (%)
n-Bu	Me	MeCOOBu-*n*	94
$PhCH_2$	Me	$MeCOOCH_2Ph$	94
s-Bu	Me	MeCOOBu-*s*	80
i-Pr	Me	MeCOOPr-*i*	82
$PhCH_2$	*n*-Pr	*n*-$PrCOOCH_2Ph$	87
$PhCH_2$	Ph	$PhCOOCH_2Ph$	53
n-Bu[a]	MeCO	MeCOCOOBu-*n*	86
n-Bu[a]	CF_3	CF_3COOBu-*n*	85

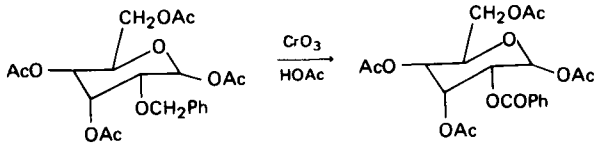
[a] These reactions did not require the addition of any mineral-acid catalyst.

palladium. Typical conversions using this approach include the reaction of methyl acetoacetate with octa-2,7-dienyl phenyl ether in the presence of bis(triphenylphosphine)palladium chloride and sodium phenoxide for two hours at 85°C to yield methyl 2-acetyldeca-4,9-dienoate and methyl 2-(octa-2,7-dienyl)-2-acetyldeca-4,9-dienoate in 84 and 7% yields, respectively, and the reaction of octa-2,7-dienyl phenyl ether with acetic acid, giving the products shown in equation (224).

$$PhOCH_2CH{=}CHCH_2CH_2CH_2CH{=}CH_2 \underset{PhOH}{\overset{AcOH}{\rightleftharpoons}} \tag{224}$$

$$MeCOOCH_2CH{=}CHCH_2CH_2CH_2CH{=}CH_2\ (85\%) + MeCOOCH(CH{=}CH_2)CH_2CH_2CH_2CH{=}CH_2\ (15\%)$$

c. With oxides of chromium. Chromium trioxide in acetic acid has been used to oxidize benzyl ethers of carbohydrates into their corresponding esters in good yields (equation 225)[634], while this same system in methylene chloride has been reported[635] to oxidize alkyl pentadecyl and alkyl hexadecyl ethers to their corresponding acids or esters (equation 226).



(50%) (225)

$$Me(CH_2)_nCH_2OCH_2R \xrightarrow[CH_2Cl]{CrO_3,\ HOAc} Me(CH_2)_nCOOR \tag{226}$$

d. With ozone, peracids and peroxides. A comprehensive study[636] of the mechanism of ozonolysis of ethers has been reported[637] where isotope-effect rate studies, competitive relative rate studies on various classes of ethers and product analysis of ozonations using ozone–oxygen and ozone–nitrogen streams have been investigated. Although the product ratios were found to vary depending upon the reaction conditions used, the major products from the reaction of ethers with ozone are esters, aldehydes and/or alcohols as shown in equations (227)–(229).

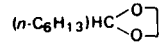
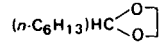
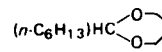
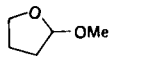
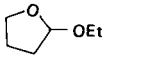
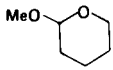
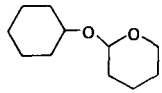
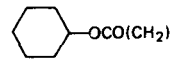
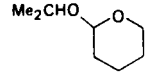
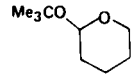
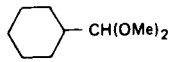
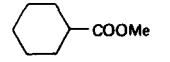
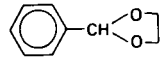
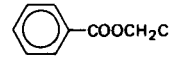
$$MeCH_2OBu\text{-}t \xrightarrow{O_3} HCOOBu\text{-}t + MeCOOBu\text{-}t + t\text{-}BuOH \tag{227}$$

$$PhCH_2OBu\text{-}t \xrightarrow{O_3} PhCOOBu\text{-}t + PhCHO + t\text{-}BuOH \tag{228}$$

$$Me_2CHOCHMe_2 \xrightarrow{O_3} MeCOMe + MeCH(OH)Me + MeCOOCHMe_2 \tag{229}$$

Esters have also been obtained[638,639] upon ozonolysis of acetals, thus ozonolysis of acyclic aldehyde acetals for two hours at room temperature in dichloromethane or ethyl acetate affords their corresponding esters in excellent yields. Cyclic acetals are converted to their corresponding esters within two hours using ozone at −78°C also in dichloromethane or ethyl acetate as solvents, while the conversion of carbohydrates to esters is best accomplished under acylation conditions, e.g. in acetic anhydride–sodium acetate for 15 hours at room temperature. Table 22 lists the various acetals which have been converted to esters using ozone[638,639]. The generality of the above reaction was demonstrated using acetals

TABLE 22. Acetals converted to esters by ozone

Acetal	Product	Yield (%)
$(n\text{-}C_6H_{13})CH(OMe)_2$ $(n\text{-}C_6H_{13})CH(OEt)_2$	$(n\text{-}C_6H_{13})COOMe$ $(n\text{-}C_6H_{13})COOEt$	90 94
	$(n\text{-}C_6H_{13})COOCH_2CH_2OH$	100
	$(n\text{-}C_6H_{13})COOCH_2CH_2CH_2OH$	97
	$(n\text{-}C_6H_{13})COOCH_2CMe_2CH_2OH$	98
	$MeCOOCH_2(CH_2)_2COOMe$	85
	$MeCOOCH_2(CH_2)_2COOEt$	87
Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside	Methyl 2,3,4,5,6-penta-*O*-acetyl-D-gluconate	95
Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside	Methyl 2,3,4,5,6-penta-*O*-acetyl-D-mannonate	74
Methyl 2,3,4,6-tetra-*O*-acetyl-β-*O*-galactopyranoside	Methyl 2,3,4,5,6-penta-*O*-acetyl-D-galactonate	92
2-Deoxy-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside	2-Deoxy-3,4,6-tri-*O*-acetyl-5-hydroxy-D-gluconate	–
	$MeOOC(CH_2)_3CH_2OH$	97–99
		91
	$Me_2CHOOC(CH_2)_3CH_2OH$	95
	$Me_3COOC(CH_2)_3CH_2OH$	91
		98
		100
Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside	Methyl 3,4,5,6-tetra-*O*-acetyl-2-deoxy-D-gluconate	81
Methyl 2,3,4-tri-*O*-acetyl-β-D-xylopyranoside	Methyl 2,3,4,5-tetra-*O*-acetyl-D-xylonate	78
Methyl 2,3,4-tri-*O*-acetyl-α-D-arabinopyranoside	Methyl 2,3,4,5-tetra-*O*-acetyl-D-arabonate	95
Methyl 2,3,4-tri-*O*-acetyl-β-D-arabinopyranoside	Methyl 2,3,4,5-tetra-*O*-acetyl-D-arabonate	71
Methyl 3,4,5-tri-*O*-acetyl-β-D-ribofuranoside	Methyl 2,3,4,5-tetra-*O*-acetyl-D-ribonate	90

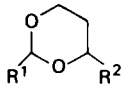
made from various aldehydes, such as *n*-heptanal, cyclohexanecarboxaldehyde and benzaldehyde, and different types of alcohols, such as methanol, ethanol, ethylene glycol, 1,3-propanediol and 2,2-dimethyl-1,3-propanediol.

Treatment of acetals with peracetic acid alone or catalysed by sulphuric acid has been found[640] to afford the corresponding ester. Reaction of crotonaldehyde di-*n*-butyl acetal with peracetic acid afforded[640] a 73% yield of *n*-butyl crotonate (equation 230), while sulphuric acid-catalysed peracetic acid oxidation of *n*-butyr-

$$MeCH{=}CHCH(OC_4H_9\text{-}n)_2 \xrightarrow[EtOAc]{MeCO_3H} MeCH{=}CHCOO(C_4H_9\text{-}n) \qquad (230)$$

aldehyde diethyl acetal gave a 69% yield of ethyl butyrate. Similar acid-catalysed oxidation of benzaldehyde diethyl acetal, β-phenyl-β-ethoxypropionaldehyde and 2-(β-styryl)-4-methyl-1,3-dioxolane afforded[640] ethyl benzoate (90%), ethyl β-phenyl-β-ethoxypropionate (61%) and propylene glycol monocinnamate (28%), respectively. Oxidation of acetals using air or oxygen to yield acids has also been reported[641].

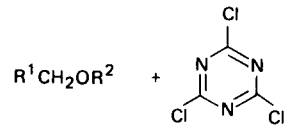
Di-*t*-butyl peroxide has also been found[642] to be effective in the oxidative isomerization of 2- and 4-substituted 1,3-dioxanes into esters and aldehydes when the reaction was performed at 90–150°C (equation 231).



$$\xrightarrow{(Me_3CO)_2} R^1COOCH_2CH_2CH_2R^1 + R^1COOCHR^2Et + EtCOR^2 + R^1CHO \qquad (231)$$

Ethers of the general formula $R^1CH_2OR^1$ have also been reported[643] to give alcohols, acids and carboxylates when treated with molecular oxygen.

e. With trichloroisocyanuric acid. A direct oxidation of aliphatic ethers of the general formula $R^1CH_2OR^1$ to carboxylic acid esters has been reported[644,645] to occur in good yield using trichloro-1,3,5-triazine (trichloroisocyanuric acid) in water at 3°C for 3–20 hours (equation 232). Using this procedure, symmetrical ethers are converted to a single ester product, whereas unsymmetrical ethers are converted to esters which are selectively determined by steric effects, namely Newman's 'rule of six'. The esters prepared by this method are shown in Table 23.

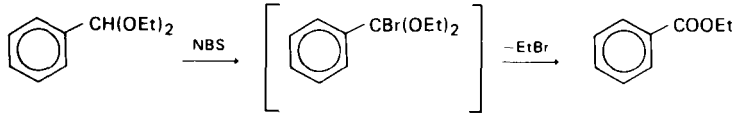


(232)

TABLE 23. Preparation of esters from ethers using trichloro-1,3,5-triazine

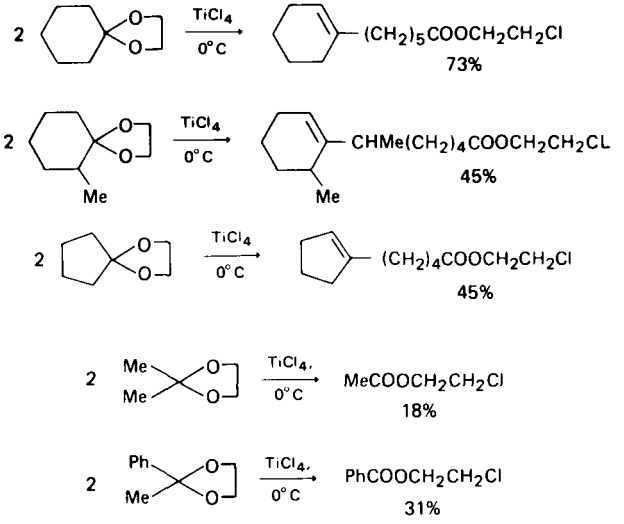
Ether	Product	Yield (%)
EtOEt	MeCOOEt	49
n-BuOBu-*n*	*n*-PrCOOBu-*n*	50–100
$PhCH_2OEt$	PhCOOEt	5
Me_2CHCH_2OEt	$Me_2CHCOOEt$	83
Me_2CHOEt	$MeCOOCHMe_2$	55

f. With inorganic and organic halides. An interesting reaction, which appears to be general for acetals, was observed[646] when benzaldehyde diethyl acetal was allowed to react with an equimolar quantity of *N*-bromosuccinimide (NBS) at 40°C. The product isolated from this reaction was ethyl benzoate suggested to be formed via the mechanism shown in equation (233).

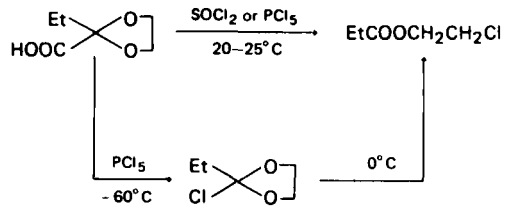


(233)

Reaction of the ethylene acetals of cyclic ketones in dichloromethane at 0°C with titanium(IV) chloride has been reported[647] to afford the 2-chloroethyl esters of a carboxylic acid containing double the number of carbon atoms of the original ketone (equation 234). It was also reported[647] that under the same conditions open-chain ketones afforded 2-chloroethyl carboxylates in which the alkoxycarbonyl group is attached to one of the 2-substituents of the original 1,3-dioxolane (equation 235). A mechanism for this series of reactions is proposed. Similar



compounds have been prepared[648] via a rather unique stereospecific reaction using thionyl chloride or phosphorus pentachloride. Thus, treatment of 2-carboxy-2-ethyl-1,3-dioxolane with either chloride at room temperature affords 2-chloroethyl propionate directly, while reaction with phosphorous pentachloride in methylene chloride at −60°C first yields 2-chloro-2-ethyl-1,3-dioxolane which rapidly rearranges to 2-chloroethyl propionate upon warming to 0°C (equation 236). The high regiospecificity and stereospecificity of this reaction can best be seen from the reaction of a 3:2 *trans*:*cis* mixture of 2-carboxy-4-methyl-2-phenyl-1,3-dioxolane with phosphorus pentachloride in methylene chloride which affords an 85–92% yield of 1-chloro-2-propyl benzoate with no trace of isomers present in the product (equation 237). Similarly, D(−)-2-carboxy-2,4,5-trimethyl-1,3-dioxolane and 2-carboxy-2,5,5-trimethyl-1,3-dioxane upon treatment with phosphorus penta-



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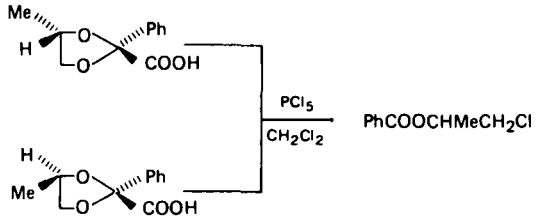
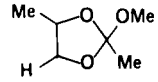
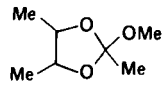
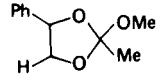
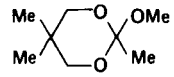
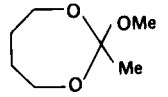
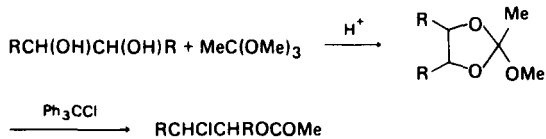


(237)

TABLE 24. Reaction of cyclic *ortho* esters with trityl chloride

ortho Ester	Product	Yield (%)
	$MeCH(OCOMe)CH_2Cl$	89
	$MeCHClCH(OCOMe)Me$	90
	$PhCHClCH_2OCOMe$	93
	$ClCH_2CMe_2CH_2OCOMe$	83
	$Cl(CH_2)_4OCOMe$	38



(238)

chloride afford L(+)-*erythro*-3-chloro-2-butyl acetate and 3-chloro-2,2-dimethylpropyl acetate, respectively.

Reaction of cyclic *ortho* esters with trityl chloride in methylene chloride at reflux has also been reported[649] to afford the acetates of the chlorohydrins in high yields (equation 238) (Table 24). These reactions were also found to be regiospecific and stereospecific, yielding the same stereochemical results as reported above in the ketal acid reaction.

g. With miscellaneous reagents. Several of the reactions discussed in this section which afford acids or esters from ethers or acetals are not oxidation reactions *per se*, but appear overall to be oxidative conversions and are thus included in this section.

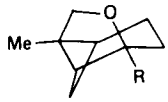
Reaction of 1-alkoxy-1,2-diacetoxyalkanes with potassium cyanide and ammonium chloride in aqueous ammonia, followed by subsequent hydrolysis of the resultant unisolated nitrile using concentrated hydrochloric acid affords α-amino-β-hydroxy carboxylic acids[650]. If primary amines are substituted for ammonia in this reaction, the corresponding α-alkylamino-β-hydroxy carboxylic acids are obtained. This overall procedure is a modification of the Strecker synthesis of amino acids and is widely applicable affording good yields for the preparation of serine and its higher homologues (Table 25).

TABLE 25. Preparation of amino acids via modified Strecker synthesis

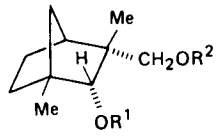
$$R^1CH(OAc)CH(OAc)OEt + H_2NR^2 + KCN \longrightarrow R^1CH(OH)CH(NHR^2)CN \xrightarrow[H_2O]{HCl} R^1CH(OH)CH(NHR^2)COOH$$

R^1	R^2	Yield (%)
H	H	51
Me	H	83
Et	H	74
n-Pr	H	67
n-$C_{10}H_{21}$	H	46
H	Me	27
H	Et	32
H	*n*-Bu	47

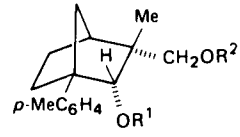
Treatment of a series of tricyclic 2,8-nopinyl ethers with a variety of reagents has lead to formation of acetate esters. Thus, treatment of 6,9-dimethyl-7-oxatricyclo[4.3.0.$0^{3,9}$]nonane (**26**, R = Me) with acetyl toluene-*p*-sulphonate in acetonitrile for 14 hours at room temperature affords[651] 80% of 1,3-dimethyl-2α-*p*-tolylsulphonyloxynorbornan-3α-ylmethyl acetate (**27**; $R^1 = SOC_6H_4Me$-*p*, R^2 = Ac). If the same starting material (**26**, R = Me) was allowed to react with boron trifluoride–etherate in acetic anhydride a 90% conversion to 2α-acetoxy-1,3-dimethylnorbornan-3α-ylmethyl acetate (**27**, $R^1 = R^2$ = Ac) was obtained[651].



(**26**)

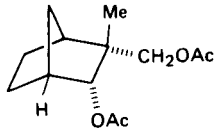


(**27**)



(**28**)

Reaction of 9-methyl-6-*p*-tolyl-7-oxatricyclo[4,3,0,$0^{3,9}$]nonane (**26**, R = C_6H_4Me-*p*) with the same reagents at 0°C for one hour afforded 3α-hydroxymethyl-3-methyl-1-*p*-tolylnorbornan-2α-yl acetate (**28**, R^1 = Ac, R^2 = H), while if the reaction was performed at −20°C followed by acetylation, using acetic anhydride in pyridine, 3α-acetoxymethyl-3-methyl-1-*p*-tolylnorbornan-2α-yl acetate (**28**, $R^1 = R^2$ = Ac) was obtained in 95% yield. The most interesting result obtained in this study[651] was the consequence of rearrangement of 9-methyl-7-oxatricyclo[4,3,0,$0^{3,9}$]nonane (**26**, R = H) to *endo*-3α-acetoxymethyl-3-methylnorbornan-2α-yl acetate (**29**) and *exo*-7-acetoxymethyl-7-methylnorbornan-2β-yl acetate (**30**) upon reaction with boron trifluoride–etherate in acetic anhydride for one hour at 0°C.



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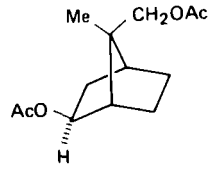
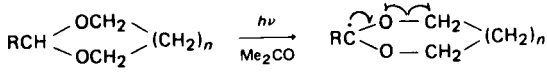


(30)

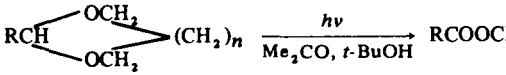
Photochemical conversions of acetals to the corresponding carboxylic esters have also been reported[652] and are shown in Table 26. These conversions may be regarded as isomerizations by an intramolecular oxidation–reduction, for which a mechanism (equation 239) was suggested where the acetone plays a vital role in the



$$\longrightarrow RCOOCH_2(CH_2)_n\dot{C}H_2 \longrightarrow RCOOCH_2(CH_2)_nMe \qquad (239)$$

initiation step, consisting of a hydrogen abstraction from the carbon attached to the oxygen atom. In the absence of acetone, rather poor yields of the esters are obtained.

TABLE 26. Preparation of esters via photochemical treatment of acetals



Acetal			
R	*n*	Product	Yield (%)
$Me(CH_2)_4$–	0	Ethyl hexanoate	36
$Me(CH_2)_6$–	0	Ethyl octanoate	55
$Me(CH_2)_8$–	0	Ethyl decanoate	33
$PhCH_2$–	0	Ethyl phenylacetate	35
$Ph(CH_2)_2$–	0	Ethyl hydrocinnamate	30–50
$Me(CH_2)_6$–	1	Propyl octanoate	23
$Ph(CH_2)_2$–	1	Propyl hydrocinnamate	14

6. Oxidation of ketones

a. With peracids (Baeyer-Villiger reaction). The Baeyer–Villiger reaction, which involves the oxidation of carbonyl compounds with a peracid, has been reviewed[652–657]. Although this reaction is applicable to both aldehydes and ketones it has been used largely with ketones and because of this fact it will be presented in this section. A variety of reagents have been used to effect ester formation from ketones, and this discussion will centre on the reagent chosen for the conversion reported.

Treatment of cyclanones in ethanol with Caro's acid affords[658] the ethyl esters of ω-hydroxy aliphatic acids with the same carbon content as the starting material albeit in fair yields. Solutions of $K_2S_2O_8$ in 50% sulphuric acid (effectively H_2SO_5) has been reported[659] to give quantitative yields of the Baeyer–Villiger products for a variety of simple aliphatic ketones. The migration aptitudes of hydrogen and simple alkyl groups in the Baeyer–Villiger oxidation of ketones has been studied[659–661] and has been found to be in the order propyl ≈ H > ethyl ≫ methyl. Peroxymonosulphuric acid (Caro's acid) has also been used to effect the Baeyer–Villiger reaction with a variety of aldehydes[423,424,434,441].

Peroxyformic acid has been found[662] an effective oxidizing agent in converting hydroxybenzaldehydes into hydroxyphenyl formates, while peracetic acid has been found to be an effective oxidizing agent under a variety of conditions. In the presence of acetic anhydride, peracetic acid treatment of salicylaldehyde affords[662] an 88% yield of *o*-hydroxyphenyl formate. Addition of a few drops of sulphuric acid to peracetic acid allows a 90% conversion[663] of benzaldehyde diethyl acetal to ethyl benzoate, while in a mixture of glacial acetic and sulphuric acids, peracetic acid oxidizes *p*-nitrobenzophenone to phenyl *p*-nitrobenzoate in 95% yield[664]. Treatment of crotonaldehyde dibutylacetal at 60°C with peracetic acid in ethyl acetate yields a 73% conversion to butyl crotonate[665]. Oxidation of cycloheptanone and cyclooctanone with peracetic acid in an inert solvent like ethyl acetate affords a good yield of the corresponding dibasic acids[666], but using the same oxidizing mixture with cyclopentanone and various cyclohexanones affords high yields of monomeric lactones. In contrast, higher ketones such as cyclododecanone are converted[667] into mixtures of lactones and dibasic acids using excess peracetic acid in acetone and sulphuric acid.

Perbenzoic acid in moist chloroform has been used to convert simple methyl ketones into their corresponding acetate esters (equation 240)[668]. Although the

$$\text{MeCOR} \xrightarrow[\text{CHCl}_3]{\text{PhCO}_3\text{H}} \text{MeCOOR} \qquad (240)$$

ketones reported above all gave good yields of ester, similar treatment of cyclopropyl methyl ketone and acetomesitylene did not afford the corresponding acetates. Treatment of propiophenone with perbenzoic acid in moist chloroform[668] affords a 73% yield of phenyl propionate, an indication that simple ketones other than methyl ketones are also susceptible to reaction. Perbenzoic acid has been used most extensively in the oxidation of steroids. The acetate of allopregnanol-3-one-20 has been converted[669] into its corresponding diacetate using perbenzoic acid, while the oxidation of 17-acetyl steroids to the corresponding 17-acetates has also been reported[670] using perbenzoic acid. Pregnane-3α-ol-11,20-dione acetate has been reported[670] to be oxidized in 85% yield to etiocholane-3α,17α-diol-11-one diacetate.

TABLE 27. Conversion of ketones to esters using trifluoroperoxyacetic acid

Ketone	Ester	Yield (%)
Methyl ethyl	Ethyl acetate	72
Diethyl	Ethyl propionate	78
Methyl *n*-propyl	*n*-Propyl acetate	78
Methyl isopropyl	Isopropyl acetate	81
Methyl *n*-butyl	*n*-Butyl acetate	81
Methyl isobutyl	Isobutyl acetate	84
Methyl *n*-amyl	*n*-Amyl acetate	87
Methyl cyclopropyl	Cyclopropyl acetate	53
Di-*n*-propyl	*n*-Propyl butyrate	80
Diisobutyl	Isobutyl isovalerate	81
Benzophenone	Phenyl benzoate	88

Although it was originally reported[652] that simple ketones of the type $R^1CH_2COCH_2R^2$ could not be oxidized to their corresponding esters with conventional reagents such as peracetic, perbenzoic or Caro's acids, trifluoroperoxyacetic acid has been shown[671] to be an effective reagent for this conversion. Oxidation of the ketones listed in Table 27 was accomplished in good yields by the addition of the ketone to a solution of peroxytrifluoroacetic acid prepared from trifluoroacetic anhydride and 90% hydrogen peroxide in methylene chloride containing disodium hydrogen phosphate. This reagent has also been used[550] in the Baeyer–Villiger oxidation of (1-methyl-*O*-carborane-3-yl)phenyl ketone which resulted in the migration of the 1-methyl-3-*O*-carboranyl group.

A similar reagent, hexafluoroacetone–hydrogen peroxide, has also been reported[672] to be effective in the oxidation of a variety of ketones to esters (Table 28).

Using a solution of 90% hydrogen peroxide in boron trifluoride etherate, a rapid conversion of simple aliphatic ketones to esters has been achieved in good yields at room temperature (Table 29)[673]. Although small amounts of the alcohols formed by hydrolysis of the esters were also obtained, the yield of esters is still acceptable. The nuclear oxidation of *m*-xylene and toluene was also effected with this reagent.

A novel reagent which has found use in the Baeyer–Villiger oxidation of ketones is permaleic acid formed[674] by reaction of maleic anhydride with hydrogen peroxide in an inert solvent. Although permaleic acid is not quite as potent a peracid as trifluoroperacetic acid and does not afford as high a yield of esters as

TABLE 28. Conversion of ketones to esters using hexafluoroacetone and hydrogen peroxide

Ketone, etc.	Ester, etc.	Yield (%)
Methyl isobutyl	Isobutyl acetate	73
Methyl *n*-amyl	*n*-Amyl acetate	81
Cyclohexanone	Caprolactone	50
Acetophenone	Phenyl acetate	34
Aniline	Nitrobenzene	65
Pentafluoroaniline	Decafluorozaobenzene	10
Mesitylene	Mesitol	40

TABLE 29. Preparation of esters using boron trifluoride and hydrogen peroxide

Ketone, etc.	Ester, etc.	Yield (%)
2-Octanone	*n*-Hexyl acetate	62
Methyl isobutyl	Isobutyl acetate	58
Diethyl	Ethyl propionate	60
2-Heptanone	*n*-Amyl acetate	60
m-Xylene	2,6-Dimethyl-3-hydroxybenzoquinone	–
Toluene	Cresol	93

indicated in Table 30, it has the advantage of being easily prepared and having a reduction product which is insoluble in the oxidation media used.

Commercially available *m*-chloroperbenzoic acid has found extensive use as the reagent of choice in the Baeyer–Villiger oxidation of steroids[422,675-679], and in the introduction of the carboxylate linkage into olefins[680]. This latter reaction involves the reaction of dicyclohexylborane with a number of olefins containing a variety of functional groups, followed by carbonylation of the resulting organoborane in water to yield a functionally substituted cyclohexyl monoalkyl ketone. Treatment of these ketones with *m*-chloroperbenzoic acid affords conversions to the corresponding substituted ester, provided the substituents do not react with any of the reagents used.

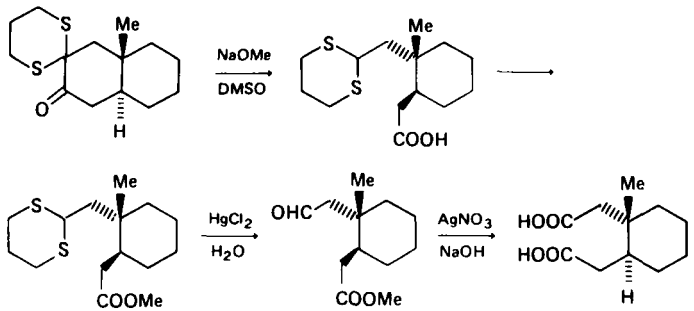
TABLE 30. Preparation of esters from ketones using permaleic acid

Ketone	Ester	Yield (%)
Methyl isobutyl	Isobutyl acetate	72
Diisobutyl	Isobutyl isovalerate	83
2-Octanone	*n*-Hexyl acetate	71
Cyclooctanone	ω-Hydroxyoctanoic acid lactone	67
Oestrone acetate	Estronolactone acetate	40
Benzophenone	Phenyl benzoate	70
Acetophenone	Phenyl acetate	70
Desoxybenzoin	Benzyl benzoate + phenyl phenylacetate (7 : 1)	75

b. With base. Reaction in the liquid phase of an α-nitro ketone with an alcohol and base affords organic esters in good yields[681]. Thus, reaction of 1-nitro-2-tridecanone with sodium methoxide for two hours under reflux produces a 90% yield of methyl dodecanoate, while reaction of 1-nitro-2-butanone with sodium isopropoxide for 16 hours at 60°C affords a comparable yield of isopropyl propionate. Other bases used include aniline, α-picoline and triethylamine, while using tertiary alcohols as solvents affords no reaction.

Using sodium methoxide in dimethyl sulphoxide causes carbon to carbon bond cleavage in the keto dithiane shown in equation (241) to afford the corresponding acid directly[682]. Conversion of the acid product to the corresponding ester followed by treatment with aqueous mercuric chloride produces the aldehyde ester, which upon treatment with basic silver nitrate gives the dibasic acid indicated[682].

When alcohol-free sodium methoxide or isopropoxide is allowed to react with α-bromo-*s*-alkyl ketones in ether as the solvent, a widely general reaction occurs which produces the ester of the tertiary acid (equation 242)[683,684]. The



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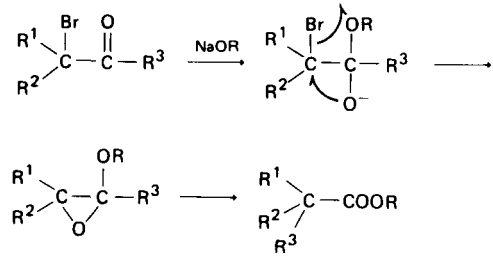


(242)

mechanism proposed for the conversion involves the intermediate formation of an ethylene oxide which then produces the ester. Reported in Table 31 are the ketones which have been found to undergo the conversion.

Reaction of an ether suspension of sodium methoxide at 10–20°C with 3,4-dibromo-3-methyl-2-butanone for 30 hours affords a mixture containing 42% of methyl β,β-dimethylacrylate and 16% methyl β-methoxyisovalerate; however with a reaction time of 2.5 hours, a mixture containing the same products but in a ratio of 64% to 2% was obtained[685]. Similarly, using the shorter reaction time 3,4-dibromo-3-methyl-2-pentanone affords 15% of 3-methyl-3-penten-2-one and 55% of methyl *trans*-3-methyl-3-pentenoate, while 1-acetyl-1,2-dibromocyclohexane affords 19% of methyl-1-cyclohexenyl ketone and 34% of methyl 1-cyclohexenyl-acetate[685].

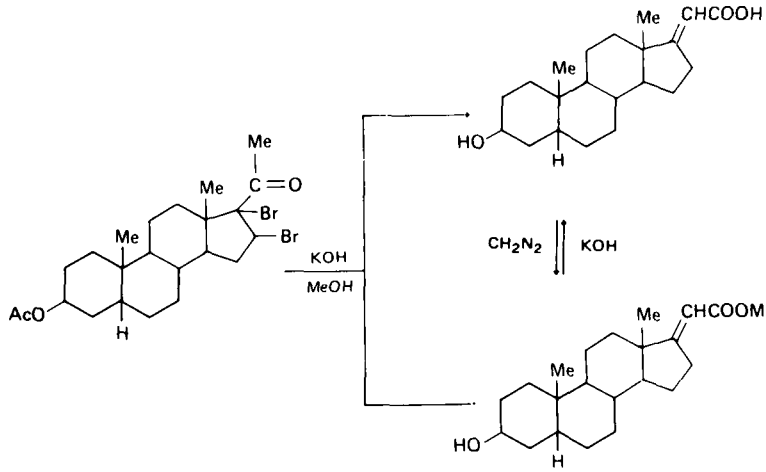
Although the most common base systems used to convert ketones into acids or esters contain alkoxides in a variety of solvents as discussed above, metal hydroxide in hexamethylphosphoramide or methanol have also been used to effect similar conversions. Using either sodium or potassium hydroxide in hexamethylphosphoramide at 23–80°C a series of C_5–C_{12} aliphatic ketones were autooxidized to their

TABLE 31. Preparation of esters from ketones using sodium alkoxides

Ketone	Base	Product	Yield (%)
3-Bromo-3-methyl-2-butanone	NaOMe	Methyl trimethylacetate	39
3-Bromo-3-methyl-2-butanone	NaOPr-*i*	Isopropyl trimethylacetate	64
3-Bromo-3-methyl-2-butanone	NaOEt	Ethyl trimethylacetate	61.3
4,4-Dimethyl-3-bromo-2-pentanone	NaOMe	Methyl methyl-*t*-butylacetate	73
3-Bromo-3-methyl-4-heptanone	NaOMe	Methyl methylethylpropylacetate	<75

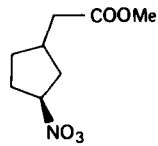
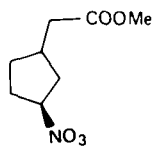
corresponding dibasic acids in moderate to excellent yields, while acetophenone afforded benzoic acid under the same conditions[686]. This study indicated that the choice of solvent for these reactions is critical and that the ease of oxidation with respect to solvent was in the order HMPA > *t*-butyl alcohol >>> water. It was also found that lithium hydroxide was not an effective base for these oxidations.

Reaction of potassium hydroxide in methanol with 16,17-dibromopregnan-3β-ol-20-one acetate has been reported to afford 3β-hydroxy-$\Delta^{17,20}$-pregnen-21-oic acid and its methyl ester by an interesting rearrangement (equation 243)[687].



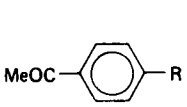
(243)

TABLE 32. Preparation of esters from cyclic ketones using ceric ammonium nitrate

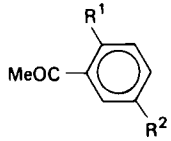
Ketones	Products	Yield (%)
Cyclohexanone	Methyl 5-nitrohexanoate	20
	Methyl 6-nitrohexanoate	30
Cyclopentanone	Methyl 5-nitropentanoate	12
	Methyl 4-nitropentanoate	8
	Methyl 4-nitrobutanoate	17
	Methyl 3-nitrobutanoate	13
Norbornanone		30
		20

c. With ceric ammonium nitrate. A study of the kinetics and mechanism of the ceric ammonium nitrate oxidation, under drastic conditions, of carbonyl compounds such as aldehydes and ketones has been reported[688]. The ultimate products from these reactions are formic acid and carbon dioxide and it appears at first glance that this oxidation is not of synthetic importance. However, treatment of cyclic ketones with four molar equivalents of ceric ammonium nitrate at 60°C in aqueous acetonitrile afforded[689] mixtures of nitrocarboxylic acids in about 50% yields as indicated in Table 32. Since these products could be treated with diazomethane, converted to their corresponding methyl esters and then separated without much difficulty, this method provides a useful approach to their preparation, albeit in low yields.

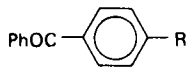
d. With nitric acid. In order to establish the structure of the various ketones prepared from Friedel–Crafts acylation of mono- and di-*s*-alkyl benzenes, oxidation to their corresponding benzene carboxylic acids was accomplished using dilute nitric acid, chromic acid or sodium dichromate–sulphuric acid–acetic acid mixtures[690]. The ketones oxidized are the acetophenones and benzophenone shown below, and with the sodium dichromate–sulphuric acid–acetic acid mixture the



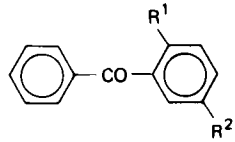
R
s-Butyl
s-Amyl
s-Octyl



R^1	R^2
Me	*s*-Butyl
s-Butyl	*s*-Butyl
s-Amyl	*s*-Amyl



R
s-Butyl
s-Amyl
s-Dodecyl



R^1	R^2
s-Butyl	*s*-Butyl

alkyl and dialkylacetophenones gave terephthalic acid. Oxidation of the dialkylacetophenones with dilute nitric acid afforded the corresponding 4-alkylisophthalic acids, while the *p*-*s*-alkylacetophenones were oxidized to their corresponding *p*-*s*-alkylbenzoic acids using nitric acid. Chromic acid oxidation converts the 2,5-di-*s*-butylacetophenone to trimellic acid, and the *p*-alkylbenzophenones and the 2,5-di-*s*-butylbenzophenone to *p*-benzoylbenzoic acid and benzoylterephthalic acid, respectively.

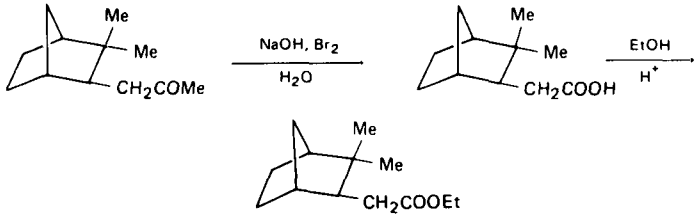
Dilute nitric acid oxidation of 4,4-diethyl-3-hexanone is reported[691] to yield a 71% conversion to 2,2-diethylbutanoic acid.

e. With alkali and halogen (haloform reaction). The haloform reaction[692] involves the conversion of the acetyl group in methyl ketones or acetaldehyde into the carboxyl group by cleavage of the acetal with halogen and a base. Various combinations of chlorine, bromine or iodine and sodium or potassium hydroxide, as their corresponding hypohalites, have been used as reagents in this reaction, and in some cases commercial bleaching agents have been used successfully. During the conversion of methyl β-naphthyl ketone to 2-naphthoic acid, which was accomplished in 87–88% yield[693], using aqueous sodium hydroxide and chlorine, it was established that excess chlorine in the hypohalite reagent is not desirable.

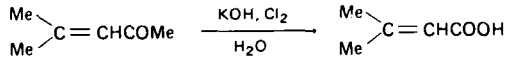
A variety of aliphatic methyl ketones have been used as starting materials in the haloform reaction and have afforded good to excellent yields of their corresponding carboxylic acids. Using aqueous sodium hydroxide and bromine as the oxidizing reagent effects the conversion of pinacolone to trimethylacetic acid (pivalic acid) in 71–74% yield[694], 4,4-dimethyl-3-ethyl-2-pentanol to ethyl-*t*-butylacetic acid in

$$t\text{-BuCHEtCH(OH)Me} \xrightarrow[H_2O]{Br_2,\ NaOH} t\text{-BuCHEtCOOH} \qquad (244)$$

38% yield (equation 244)[695] and 1-(2,2-dimethyl-3-norbornyl)propanone to 3-carboxymethylene-2,2-dimethylnorbornane which was then converted into its ethyl ester in 80% yield (equation 245)[696]. That the presence of unsaturation does not affect the course of the haloform reaction is illustrated by the conversion of mesityl oxide to β,β-dimethylacrylic acid in 49–53% yield using potassium hydroxide and chlorine (equation 246)[697].

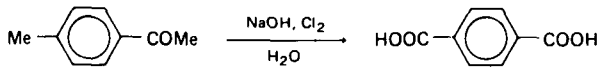


(245)

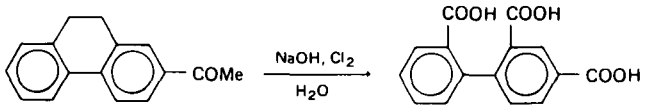


(246)

The only complication which arises when aryl methyl ketones are used in the haloform reaction occurs when methylene or methyl groups are attached to the aromatic nucleus. In these cases the methylene or methyl group as well as the acetyl group are oxidized to carboxyl groups. Thus, *p*-methylacetophenone affords terephthalic acid in 47% yield (equation 247), while 2-acetyl-9,10-dihydrophenanthrene affords 2,2′,4-tricarboxylbiphenyl in 49% yield (equation 248)[698]. Aside

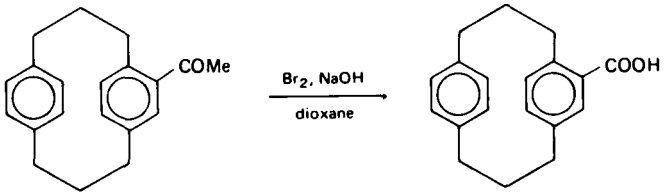


(247)



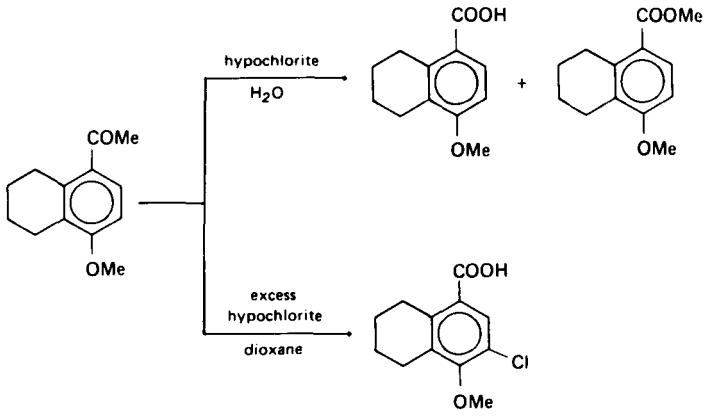
(248)

from this difficulty, the oxidation of other simple or substituted aryl methyl ketones via the haloform reaction occurs in the usual manner. Treatment of acetophenone with chlorine affords dichloroacetophenone which upon treatment with aqueous sodium hydroxide affords a 76–87% yield of mandelic acid[699]. Reaction of *p*-bromoacetophenone with bromine affords *p*,α,α-tribromoacetophenone, which upon treatment with aqueous sodium hydroxide affords[700] *p*-bromomandelic acid in 69–83% yield. Alicyclic groups do not change the course of reaction, since treatment of 5-acetyl[3.3]paracyclophane in dioxane with bromine and aqueous potassium hydroxy affords 5-carboxy[3.3]paracyclophane in 96% yield (equation 249)[701], and treatment of 5-acetyl-8-methoxytetralin with calcium hypochlorite in aqueous potassium hydroxide affords 8-methoxy-5-tetralincarboxylic acid along with its corresponding methyl ester, 5-carbomethoxy-8-meth-



(249)

oxytetralin (equation 250)[702]. If excess hypohalite in dioxane is used in the latter reaction, chlorination of the aromatic nucleus occurs affording 7-chloro-8-methoxy-5-tetralincarboxylic acid.



(250)

Alkyl ketones which are higher than methyl have also been reported to undergo the haloform reaction as long as there are two α-hydrogen atoms present. Thus, propiophenone affords a 64% yield of benzoic acid when treated with bromine and aqueous sodium hydroxide[703,704]. During the investigation of the mechanism of this conversion[704] 1-phenyl-1,2-propanedione was also allowed to react with this mixture of reagents and a 91% conversion to benzoic acid was obtained.

Heterocyclic molecules have also been reported to undergo typical haloform reactions, such as the conversion of *n*-propyl 2-thienyl ketone to 2-thiophenic acid[703], 5-methyl-2-propionylthiophene to 5-methyl-2-thiophenic acid (67%)[703], and 2-acetyl-5-*n*-butylpyridine ketone to 5-*n*-butylpyridine-2-carboxylic acid (90%)[705].

Both aliphatic and alicyclic β-diketones have been treated under haloform reaction conditions and the results obtained are interesting. Since aliphatic β-diketones cleave under the conditions of the haloform reaction, they are converted to carboxylic acids according to equation (251). On the other hand, cyclic

$$R^1OC-CH_2COR^2 \xrightarrow[H_2O]{X_2,\ NaOH} R^1COOH + R^2COOH \qquad (251)$$

β-diketones afford diacids upon treatment with alkali and halogen, for example treatment of methone (5,5-dimethyl-1,3-cyclohexanedione) with aqueous sodium hydroxide and chlorine gives an 81–91% yield of β,β-dimethylglutaric acid[706].

Other more interesting examples of the haloform reaction include the conversion of 1,1′-diacetylferrocene to ferrocene-1,1′-dicarboxylic acid in 85–90% yield using

sodium hypobromite in aqueous dioxane at 0–5°C[707], the conversion of the methyl ketone formed by ozonolysis of hardwickiic acid to its corresponding carboxylic acid using sodium hypobromite[578], and the conversion of 3β-acetoxy-5-pregnen-20-one (pregnenolone acetate) to 3β-acetoxyetienic acid (3β-acetoxy-5-androstene-17β-carboxylic acid) in 55–63% yield also using sodium hypobromite[708].

Limited bromination of methyl ketones, followed by reaction with potassium bicarbonate affords *cis*-α,β-unsaturated acids (equation 252)[709].

$$RCH_2COMe \xrightarrow{Br_2} RCHBrCOCH_2Br \xrightarrow[2.\ HCl]{1.\ KHCO_3} \begin{matrix} R & & COOH \\ & C=C & \\ H & & H \end{matrix} \qquad (252)$$

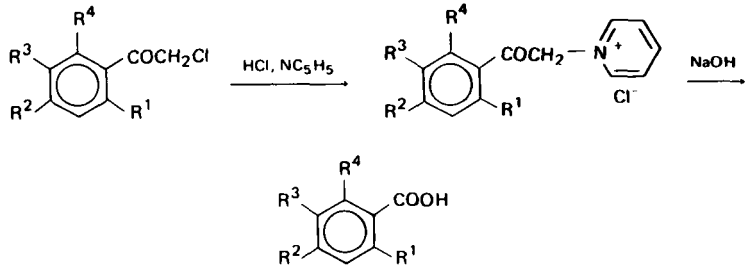
f. With iodine–pyridine and alkali. An alternative method to the haloform reaction for the conversion of acetyl groups into carboxyl groups has been reported[710], which involves the reaction with iodine in the presence of the base, pyridine. This reaction (equation 253), which gives good yields of carboxylic acid

$$ArCOMe \xrightarrow[C_5H_5N]{I_2} (ArCOCH_2\overset{+}{N}C_5H_5)I^- \xrightarrow[2.\ H^+]{1.\ NaOH} ArCOOH \qquad (253)$$

products, has been found effective in cases where the haloform reaction cannot be used, such as in the preparation of a variety of aromatic[710] and hydroxybenzoic acids[711]. Its mechanism parallels that of the haloform reaction[710,711] and involves substitution of iodine for an α-hydrogen to produce the α-pyridinium iodide salt ($ArCOCH_2\overset{+}{N}C_5H_5I$) which is attacked by the hydroxide ion to give an anion which then cleaves to produce the carboxylic acid.

Some examples of the use of this reaction include the preparation of: 1-naphthoic acid in 90% yield from 1-acetylnaphthalene[710], 5-indanecarboxylic acid in 75% yield from 5-acetylindane[712], and 6-carboxydehydroabietic acid in 70–80% yield from methyl 6-acetyldehydroabietate[713].

Treatment of methoxy-substituted ω-chloroacetophenones with pyridine hydrochloride affords a double transformation converting the chloroacetyl group into a pyridinioacetyl group while the methoxy groups are cleaved to hydroxy groups. Treatment of the resulting product with boiling aqueous sodium hydroxide effects degradation of the pyridinioacetyl group to a carboxyl group (equation 254)[714].



(254)

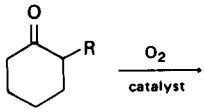
g. With oxygen, ozone, peroxide or air. Liquid-phase oxidation of a series of methyl alkyl and dialkyl ketones of the general formula shown in equation (255),

$$R^1CH_2COCH_2R^2 \xrightarrow[O_2]{120-140^\circ C} R^1COOH \qquad (255)$$

TABLE 33. Oxidation of α-alkylcyclohexanones using oxygen

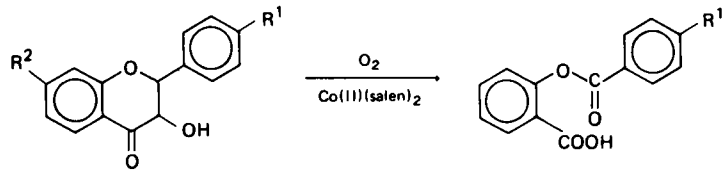
R	Catalyst	Yield (%)	Reference
Me	EtOH + NaOH	18	716
Me	KF	63	717
Me	LiF	14	717
Me	none	<1	717
Me	NaF	<5	717
Cyclohexyl	EtOH + NaOH	–	716
Cyclohexyl	KF	40	717

at 120–140° and 15 kg/cm^2 of oxygen pressure, produced the corresponding carboxylic acids in yields ranging from 72–83% via radical attack at the CH_2 group alpha to the carbonyl group[715]. Oxidation of α-alkyl-substituted cyclohexanones using oxygen has been accomplished using ethanolic sodium hydroxide[716] or fluorides of potassium, lithium, cesium or rubidium[717] as catalysts (Table 33) (equation 256). In a similar manner oxygen oxidation of 2-isopropyl-5-methylcyclohexanone afforded 3,7-dimethyl-6-oxooctanoic acid[716]. Cobalt or manganese acetate-catalysed oxygen oxidation of cyclooctanone or cyclododecanone in acetic acid gave suberic acid (65%) and 1,12-dodecanedioic acid, respectively[718].



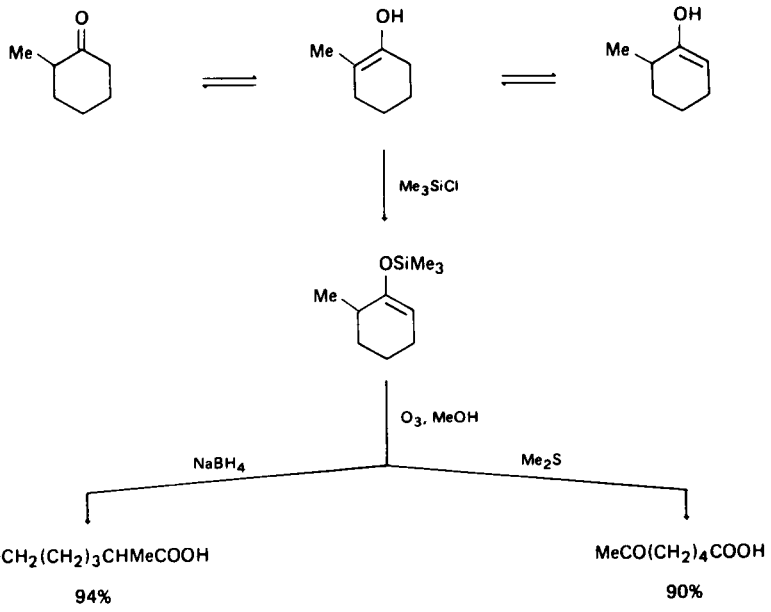
$$RCO(CH_2)_4COOH \qquad (256)$$

Recently, bis(salicylidene)ethylenediaminatocobalt(II) [Co(salen)$_2$] has been reported[719] to catalyse the oxygen oxidation of 3-hydroxyflavones in dimethylformamide or dimethylsulphoxide, but not in methanol, tetrahydrofuran or methylene chloride, giving rise to oxidative cleavage of the heterocyclic ring of the flavones affording the corresponding depsides in excellent yields (equation 257).

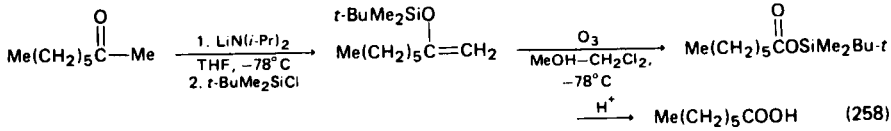


(257)

Although ozone is not a commonly used reagent for the oxidation of ketones *per se*, it has been used to oxidize ketone derivatives to carboxylic acids. Ozonolysis of silyoxyalkenes, which are generated from ketones by trapping the kinetic or thermodynamic enolate with a trialkylsilyl chloride or by trapping the kinetic enolate generated in the conjugate addition of organometallic reagents to enones, followed by a workup of the ozonolysis product with sodium borohydride affords hydroxy acids. If the ozonolysis product is worked up using dimethylsulphide then keto acids are obtained[720]. This overall two-step process (Scheme 5) of forming and cleaving the kinetic enolate provides a method of oxidatively cleaving an unsymmetrical ketone away from the more highly alkylated side of the molecule. This method has also been applied[720] to acyclic ketones as shown in equation (258). It has also been observed[720] that the oxidation of silylated ketone acetals

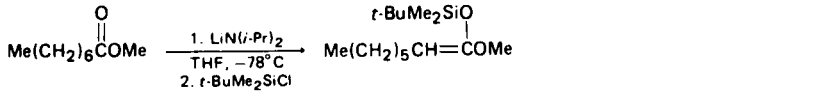


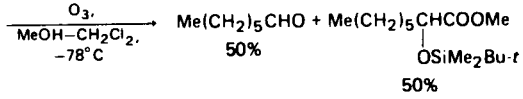
SCHEME 5.



(258)

can lead to anomalous results (equations 259 and 260). A mechanism for this mode of reaction is presented[720].





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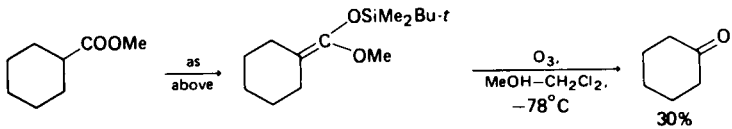
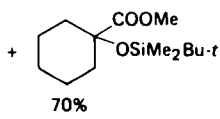
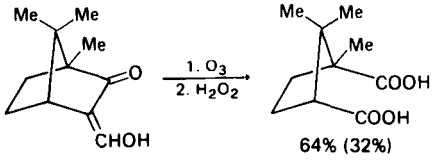


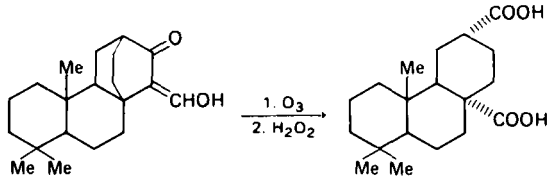


(260)

Although oxidative ozonolysis of hydroxymethylene ketones leads to diacids these products are contaminated with large amounts of anhydrides. However if a basic hydrolysis step is included during the workup an improvement in the yields of the diacids formed is realized[721,722]. Examples of diacids prepared by this improved procedure are given in equations (261) and (262), with the yields in parentheses representing the results obtained without inclusion of the basic hydrolysis step.



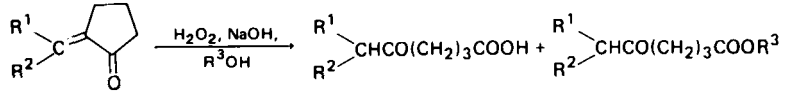
64% (32%) (261)



68% (44%) (262)

Conversions of keto steroids into carboxy steroids using ozone have also been reported[723].

Solutions of hydrogen peroxide containing a variety of catalysts have been used to prepare mono- and dicarboxylic acids from acyclic ketones. Using a solution of hydrogen peroxide in *t*-butyl alcohol containing 2 mole % of selenium dioxide at 80°C for two hours has effected oxidative ring-contractions of cycloheptanone, cyclohexanone and cyclopentanone to cyclohexane-, cyclopentane- and cyclobutanecarboxylic acids in 34, 32 and 23% yields, respectively[724]. With 30% hydrogen peroxide containing sodium hydroxide a variety of α,β-unsaturated carbonyl compounds have been converted to mono- and dicarboxylic acids as indicated in Table 34[725], while using the same oxidizing mixture in an alcohol converts a series of 2-alkylidenecyclopentanones into a mixture of 5-oxoalkanoic acids and their corresponding esters (equation 263)[726]. From this reaction the

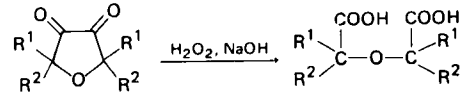


(263)

TABLE 34. Preparation of carboxylic acids from α,β-unsaturated carbonyl compounds using hydrogen peroxide

α,β-Unsaturated carbonyl compounds	Product	Yield (%)
2-Cyclohexen-1-one	Glutaric acid	72
1-Acetyl-1-cyclohexene	Adipic acid	67
Isophorone	3,3-Dimethyl-5-ketohexanoic acid	84
Pulegone	3-Methyladipic acid	60
Verbenone	Pinononic acid (1 : 1 *cis,trans* mixture)	85
Citral	2-Methyl-2-hepten-6-one	77
5,5-Dimethyl-1,3-cyclohexanedione	3,3-Dimethylglutaric acid	80

yields of acids are in the range of 25% while the yields of ester are in the range of 60%. A comparable reaction mixture has been reported[727] to effect the conversions shown in equations (264) and (265).



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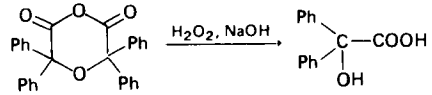
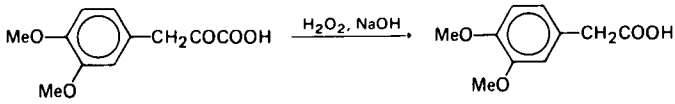


(265)

Hydrogen peroxide in the presence of alkali has also been used to prepare carboxylic acids from α-keto acids and α-keto esters. The preparation of 3,4-dimethoxyphenylacetic acid (equation 266)[728] and 9-fluorenecarboxylic acid (equation 267)[729] are typical of such reactions.



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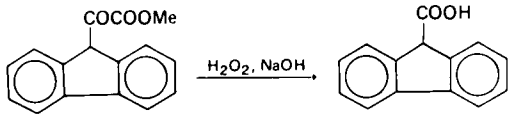


(267)

The application of cycloalkanone peroxides in the synthesis of various types of carboxylic acids has been reviewed[730]. An example of this type of reaction is illustrated by the preparation of 6-hydroxycaproic acid and adipic acid from cyclohexanone upon treatment with cyclohexanone hydroperoxide[731].

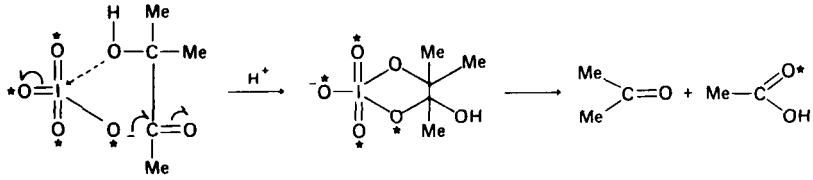
Aromatic carboxylic acids have also been prepared via air oxidation of alkyl aryl ketones in water and in the presence of a promoting agent such as copper(I) chloride[732]. Using this method benzoic, *o*- and *p*-toluic and 2-naphthoic acids have been prepared from acetophenone, *o*- and *p*-methylacetophenone and 2-acetonaphthalene, respectively.

h. With periodate. The use of periodate as an oxidizing agent has been reviewed at least seven times[325,733-738], the first review[733] being published in 1928, and the latest review[325] being published in 1974.

A variety of aliphatic, aromatic and alicyclic mono- and diketones have been oxidized by periodate to afford the corresponding carboxylic acids. A study[739] of the mechanism of periodate oxidation has been published using ^{18}O as a tracer in ^{18}O-labelled periodate. When this reagent was used in the oxidation of methylacetoin (3-hydroxy-3-methylbutan-2-one), acetone and acetic acid were the products isolated, and it was established that the oxygen of the acetone came from the hydroxyl group of the hydroxy ketone starting material and that the additional oxygen atom of the acetic acid came from the periodate according to the mechanism shown in equation (268)[740]. Other aliphatic ketones which have been treated with periodic acid or periodates and converted to their corresponding carboxylic acids are shown in Table 35.

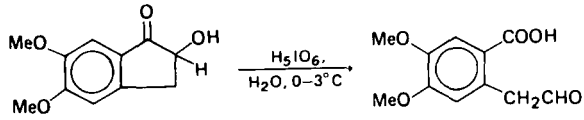
TABLE 35. Preparation of carboxylic acids from ketones using periodic acid or periodates

Ketone	Reagent	Product	Reference
Benzoin	$NaIO_4$ + NaOH	Benzilic acid	741
Benzoin	$NaIO_4$ + H_2SO_4	Benzoic acid	742
Acetoin	$NaIO_4$ + H_2SO_4	Acetic acid	742
Methylglyoxal	$NaIO_4$ + H_2SO_4	Formic acid + acetic acid	742
p-Toluoylphenylcarbinol	$NaIO_4$ + H_2SO_4	*p*-Toluic acid	742
Dihydroxyacetone	$NaIO_4$ + H_2SO_4	Glycollic acid	742
3,5-Dehydroxy-2-carboxybenzoyl methyl ketone (hydrate)	$NaIO_4$ + H_2SO_4	3,5-Dihydroxyphthalic acid	742
Benzfuroin	$NaIO_4$ + H_2SO_4	Pyromucic acid	742
3,5-Dihydroxy-2-carboxyphenyl-acetylcarbinol	$NaIO_4$ + H_2SO_4	6-Aldehydo-2,4-dihydroxybenzoic acid + acetic acid	742
2-Hydroxymethylenecyclohexanone	$NaIO_4$	Adipic acid	743



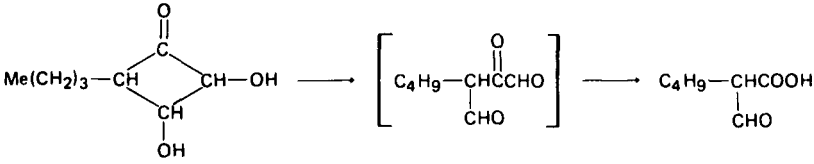
(268)

One of the largest classes of compounds which have been oxidized to acids using periodates and periodic acids are α-hydroxy cyclic ketones. Oxidation of 2-hydroxyindan-1-one derivatives with cold periodic acid produces *o*-carboxyphenylacetaldehydes in high yields[744], thus periodic acid oxidation of 2-hydroxy-5,6-dimethoxyindane-1-one in water at 0–3°C afforded 2-carboxy-4,5-dimethoxyphenylacetaldehyde in 90% yield (equation 269). Tetrahydroterrein, the reduction



(269)

product of terrein, has been reported[745] to produce its corresponding aldehydic acid upon treatment with periodic acid, probably via the intermediate ketoaldehyde (equation 270).



(270)

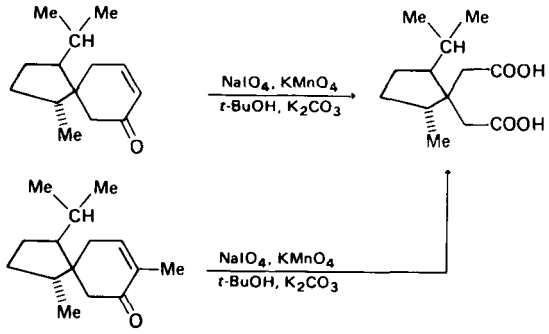
Both 1,2- and 1,3-diketones yield carboxylic acids upon periodate oxidation. For example, biacetyl(butane-2,3-dione) has been oxidized by basic solutions of ^{18}O-labelled periodate[739] affording acetic acid in which the additional oxygen atom of the acetic acid comes from the periodate. This oxidation was also performed using acidic periodate[742] and acetic acid was again obtained. Other diketones which have been converted to carboxylic acids using periodates[746]

TABLE 36. Conversion of diketones to acids using periodates

Diketone	Acid obtained	Yield (%)
1,3-Cyclohexanedione	Glutaric	86.5
5-Methyl-1,3-cyclohexanedione	3-Methylglutaric	90
5,5-Dimethyl-1,3-cyclohexanedione	3,3-Dimethylglutaric	92
1,3-Indandione	Succinic	–
1,3-Indandione	Phthalonic +	18.3
	phthalic	18.5
2-Methyl-1,3-cyclohexanedione	Acetic +	94
	glutaric	59
2-Ethyl-1,3-cyclohexanedione	Propionic +	90
	glutaric	68
2-Benzyl-1,3-cyclohexanedione	Phenylacetic +	85
	glutaric	73

include benzil which affords benzoic acid[742] and the cyclic 1,3-diketones[747] shown in Table 36. In addition, the reaction of periodate ion with the three acyclic 1,3-diketones, 2,4-pentanedione, 1-phenyl-1,3-butanedione and 1,3-diphenyl-1,3-propanedione, was observed to occur only very slowly, if at all[747]. These results and others led to the conclusion[747] that five- or six-membered cyclic 1,3-diketones which are unsubstituted on $C_{(2)}$ reduce four molar equivalents of periodate and afford one equivalent of carbon dioxide and one equivalent of a dibasic acid, while six-membered cyclic 1,3-diketones which are substituted on $C_{(2)}$ reduce three molar equivalents of periodate and afford one equivalent of a monobasic acid and one equivalent of a dibasic acid. Postulated reaction intermediates and the mechanism are also presented.

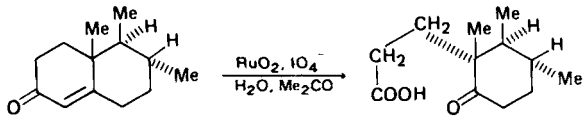
Reports of the use of periodate as a cooxidant in conjunction with a variety of other compounds for the oxidation of ketones to carboxylic acids have also appeared in the literature. Of these other materials, potassium permanganate (Lemieux–von Rudloff reagent) appears to be the most widely used. Although α,β-unsaturated keto steroids have been the most widely oxidized[555,748] class of compounds using this combination of reagents, the stereoisomeric spiro[4.5]decanone derivatives shown in equations (271) and (272) have also been converted[749] to their corresponding dicarboxylic acids using mixtures of sodium periodate and potassium permanganate in *t*-butanol containing potassium carbonate.



(271)

(272)

Another material which is used with periodate as a cooxidant is ruthenium dioxide[497]. Reaction of sodium periodate and ruthenium dioxide generates ruthenium(VIII) oxide *in situ*, and addition of sodium periodate during the reaction regenerates the tetroxide. This reagent is useful for cleavage of conjugated and cross-conjugated steroidal ketones (equation 273)[497]. Thus, testosterone is

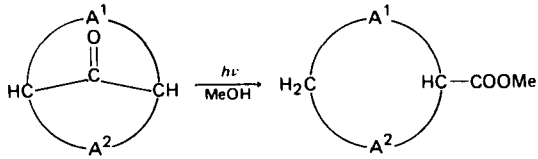


(273)

converted to its keto acid in 80% yield[497]. Using this reagent mixture to oxidize oestradiol diacetate affords[497] 3,17β-diacetoxy-9α-hydroxy-6-oxooestra-1,3,5(10)-triene in 40% yield via an interesting double allylic oxidation.

i. With light (photochemically). The light-induced formation of acids from cyclic ketones has been thoroughly reviewed[750] through 1963, and the information contained in this review will not be repeated.

By the reaction of cyclic ketones with ω,ω'-dihaloalkanes the carbonyl-bridged cycloalkanes shown in equation (274) are obtained[751], which upon photolysis in methanol afford the corresponding methyl cycloalkanecarboxylates.



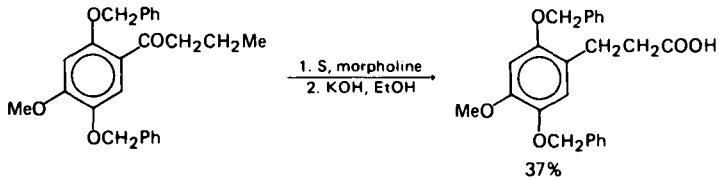
(274)

A^1	A^2	Yield (%)
$-(CH_2)_9-$	$-(CH_2)_4-$	73
$-(CH_2)_{10}-$	$-(CH_2)_3-$	55
$-(CH_2)_{10}-$	$-CH_2-CHMeCH_2-$	33

j. With sulphur (Willgerodt reaction). The Willgerodt reaction, which consists of the conversion of a straight- or branched-chain aryl alkyl ketone into an amide and/or the ammonium salt of an acid using ammonium polysulphide (equation 275), has been reviewed[752,753]. The carbonyl group of the product always occurs

$$ArCOCH_2Me \xrightarrow{(NH_4)_2S_x} ArCH_2CH_2COOH + \text{amide} \qquad (275)$$

at the end of the chain, and yields decrease sharply with increasing chain length. If sulphur and a dry primary or secondary amine are used as the reagents the reaction is called the Kindler modification[754] of the Willgerodt reaction and the products obtained in this case are alkylthioamides which can be hydrolysed to their corresponding acids. A more recent example[755] of this reaction is shown in equation (276).



37%

(276)

k. With miscellaneous reagents. Reaction of a variety of ketone hydrazones with lead tetraacetate has recently been reported[756–758] to effect good conversion to carboxylic acid esters. The extent of the conversion and the versatility of the reaction is demonstrated by the results shown in Table 37.

Preparation of substituted benzoylformic acids has recently been accomplished[759–761] by the potassium permanganate oxidation of the corresponding

TABLE 37. Oxidation of ketone hydrazones to esters using lead tetraacetate

Hydrazone of	Product	Yield (%)
3β-Hydroxylanostan-7-one	3β-Acetoxylanost-7-ene + 3β;7α-diacetoxylanostan	20 68
3β-Hydroxylanost-24-en-7-one	3β-Hydroxylanosta-7,24-diene + 3β-hydroxy-7α-acetoxylanost-24-ene	20 68
Benzophenone + dimethylacetylenedicarboxylate	3,4-Diphenylpyrazole-5-carboxylic acid	84
Dicyclohexyl ketone	Dicyclohexylmethyl acetate	46
Dicyclohexyldiazomethane	Dicyclohexylmethyl acetate	26
17β-Acetoxy-5α-androstan-3-one	5α-Androstan-3α,17β-diol diacetate + 5α-androstan-3β,17β-diol diacetate	32.4 19

substituted acetophenones in pyridine at 10°C (equation 277), while treatment of acetophenones in acidic methanol with *thallium(III) nitrate affords*[762] methyl phenylacetates via a simple one-step conversion (equation 278). Thallic ion in perchloric acid has also been used to effect[756] ring-contractions of cycloalkanones to cycloalkanecarboxylic acids. The contractions effected using this method are: cyclohexanone to cyclopentanecarboxylic acid, 3-methylcyclohexanone to 2-methylcyclopentanecarboxylic acid, 4-methylcyclohexanone to 3-methylcyclopentanecarboxylic acid and 2,2-dimethylcyclohexanone to 2,2-dimethylcyclopentanecarboxylic acid.

$$\mathrm{ArCOMe} \xrightarrow[C_5H_5N]{KMnO_4} \mathrm{ArCOCOOH} \qquad (277)$$

$$\mathrm{ArCOMe} \xrightarrow[HClO_4,\ MeOH]{Tl(NO_3)_3} \mathrm{ArCH_2COOMe} \qquad (278)$$

The transformation of an aromatic carboxylic ester into a chain-extended aromatic carboxylic ester containing additional functional groups has been reported[757] via an intermediate β-keto sulphoxide. Thus, condensation of esters with dimethylsulphoxide in basic solution gives the corresponding β-keto sulphoxides (equation 279), which upon treatment with a basic solution of bromine afford

$$\mathrm{ArCOOR} + \mathrm{Me_2SO} \xrightarrow{KOBu\text{-}t} \mathrm{ArCOCH_2SOMe} \qquad (279)$$

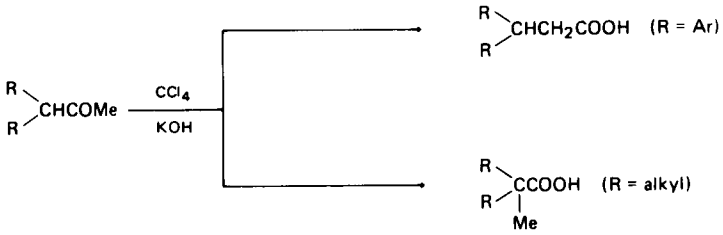
Ar	Yield (%)
Ph	88
p-MeC_6H_4	87
p-$MeOC_6H_4$	95
p-BrC_6H_4	79
α-$C_{10}H_7$	95
β-$C_{10}H_7$	91

$$ArCOCH_2SOMe \xrightarrow[base]{Br_2} ArCOCHBrSOMe \quad (280)$$

$$ArCOCHBrSOMe \xrightarrow{ROH} ArCOCOOR \quad (281)$$

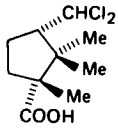
α-bromo-β-keto sulphoxides (equation 280). Treatment of these α-bromo-β-keto sulphoxides with alcohols affords the corresponding esters (equation 281).

Reaction of ketones containing α- but no α′-hydrogens with potassium hydroxide solutions of carbon tetrachloride results[758] in poly-α-chlorinated products which are subsequently cleaved via the haloform reaction to carboxylic acids. However, reaction of the same reagents with ketones containing α- and α′-hydrogens transforms them *in situ* into the carboxylic acids expected to be formed via the Favorskii reaction on the corresponding α-chloro ketones (equation 282) (Table 38)[758].



(282)

TABLE 38. Preparation of carboxylic acids from ketones using potassium hydroxide

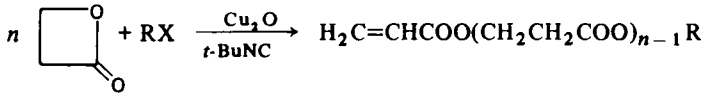
Ketones	Product	Yield (%)
Me_3CCOMe	Me_3CCOOH	80
Camphor		70
$Ph_2CHCOMe$	Ph_2CHCH_2COOH	70
$Me_2CHCOMe$	Me_3CCOOH + $Me_3CCOOCMe_3$	70 20–50

7. *Oxidation of Amines and Lactones*

Reaction of 3-hydroxyldialkylamines, which can be formed from a Mannich reaction[766], with sodium periodate[767] affords a number of cleavage products including carboxylic acids (equation 283). Similar reactions with 1-phenyl-2-piperidinoethane and 1-phenyl-2-morpholinoethane gave[767] phenylacetic acid in both cases.

$$PhCH(OH)CH_2CH_2NEt_2 \xrightarrow{NaIO_4} PhC(OH)CH_2COOH \quad (283)$$

TABLE 39. Preparation of acrylates from β-propiolactone and alkyl halides



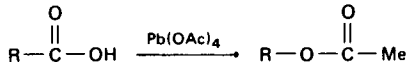
R	X	Yield (%)		
		$n = 1$	$n = 2$	$n = 3$
$MeOCCH_2-$	Cl	35	26	2
$n\text{-}C_4H_9-$	I	30	27	11
$s\text{-}C_4H_9-$	Br	9	29	11
$PhCH_2-$	Br	15	5	–
$CNCH_2-$	Cl	20	–	–

Heating β-propiolactone with alkyl halides in the presence of copper(I) oxide and *t*-butyl isocyanide as catalysts results[768] in the formation of an oligomer mixture of acrylates (Table 39).

8. *Oxidation of acids*

The interconversion of one acid into another acid or ester via oxidation has been accomplished using a variety of reagents.

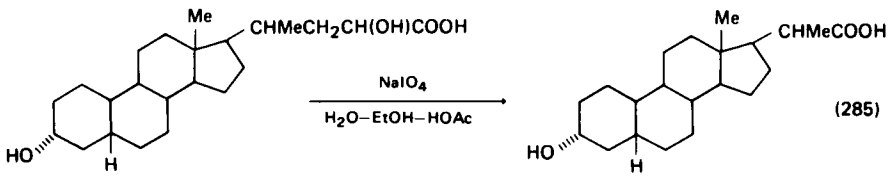
Oxidative decarboxylation of acids by lead tetraacetate[769] converts the original acid into an acetate ester under the conditions of the reaction (equation 284).



(284)

Using potassium permanganate in base converts[770] oleic acid into a mixture of 9-hydroxy-10-ketostearic and 10-hydroxy-9-ketostearic acids, while using the same reagent, elaidic acid is converted[770] into a mixture of the two hydroxyketo stearic acids mentioned above and 9,10-dihydroxystearic acid. With chromic acid in glacial acetic acid, 9-hydroxy-10-ketostearic acid is converted[770] into stearoxylic acid, while acidic potassium permanganate converts[770] nonanoic acid into a mixture of azelaic acids.

Periodate oxidation of α-hydroxy bile acids causes Barbier–Wieland degradation[771] into another acid. Thus, reaction of 3α,23-dihydroxycholanic acid in water–ethanol–acetic acid with sodium periodate affords norcholanic acid (equation 285)[772].



(285)

Oxidation via anodic electrolysis has also been found[773] to convert acids into esters, since electrolysis of mono- and diphenylacetic acids in acetic acid solution affords benzyl and diphenylmethyl acetates both in about 40% yield.

H. Acids by Cleavage Reactions

Carboxylic acids are obtained as products from the cleavage of a variety of other functional groups using a variety of reagents. The most common functional groups which produce acids upon cleavage are ethers and ketones, and a discussion of the cleavage reactions these groups undergo will be presented in this section.

1. *Of ethers*

The cleavage reactions of ethers, many of which lead to carboxylic acids, were reviewed by Burwell[774] in 1954. More recently however, aqueous bromine has been reported[775] to react with a wide variety of aliphatic ethers at 25°C via an oxidative cleavage mechanism to afford carboxylic acids. In addition to a determination of the products and yields which are shown in Table 40, this report[775] also investigated the determination of the rate law and the pH-rate profile for this cleavage.

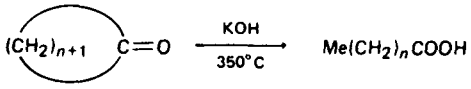
TABLE 40. Preparation of acids from ethers using bromine

Ether	Acid product	Yield (%)
Diethyl	Acetic	100
Dipropyl	Propionic +	95
	α-bromopropionic	5
Dibenzyl	Benzoic +	55
	4-bromobenzoic	45
4-Nitrobenzyl methyl	4-Nitrobenzoic	68

Another recent approach to the production of carboxylic acids via cleavage reactions involves the alkali fusion of long-chain unsaturated fatty acids[776–779], keto and hydroxy acids[776–780], acids with vicinal oxygen functions[776,777], and epoxy and alkoxy acids[781]. This latter approach affords a series of mono- and dicarboxylic acids from several different starting ethers. Thus, potassium hydroxide fusion of *cis*- and *trans*-9,10-epoxyoctadecanoic acids and *threo*- and *erythro*-9,10-dihydroxyoctadecanoic acids at 300°C for one hour affords octanoic, nonanoic and nonanedioic acids in roughly equimolar amounts[781]. Other acids cleaved[781] by alkali fusion include: 10,11-epoxyundecanoic acid, *cis*-9,10-*cis*-12,13-diepoxyoctadecanoic acid, 9,10,12,13-tetrahydroxyoctadecanoic acid, 9,12-dioxooctodec-10-enoic acid, 10,11-epoxy-12-oxooctadecanoic acid and a series of 11-alkoxyundecanoic acids.

2. *Of ketones*

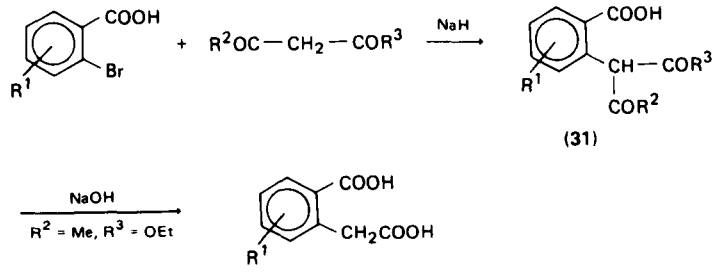
Cleavage of ketones to produce acids and/or esters is usually accomplished with strong bases such as *t*-butoxide; however several examples have been reported where milder hydroxide bases have been used. Potassium hydroxide in olefin-free petroleum oil at 350°C has been used to effect ring-opening of cyclic ketones affording monocarboxylic acids (equation 286)[782]. The reactions were performed on ketones with $n = 4$ to $n = 10$ and the yields of acid increased rapidly from $n = 4$, where practically no ring-opening was observed, to $n = 10$ where a 55% yield was achieved.



(286)

Treatment of 2,2′-sebacoyldicyclohexanone with an ethanolic solution of sodium hydroxide affords disodium 7,16-diketodocosanedioate which upon reaction with hydrazine hydrate and potassium hydroxide in triethanolamine affords a 69–72% yield of docosanedioic acid[783].

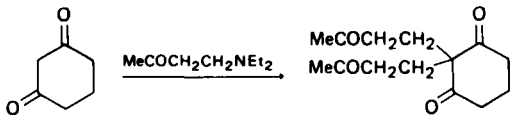
Reaction of a variety of substituted 2-bromobenzoic acids with β-keto esters in the presence of sodium hydroxide at 60–80°C using copper bromide as a catalyst affords[784] the corresponding α-acylhomophthalic acid half-esters (31) which upon hydrolysis with 2 N sodium hydroxide at room temperature produce[784] the substituted homophthalic acids (32) shown in equation (287).



(287)

			Yield (%)	
R^1	R^2	R^3	31	32
H	Me	Me	91	
H	Me	OEt	96	92
H	OEt	OEt	92	
H	Ph	OEt	98	
4-Me	Me	Me	82	
4-Me	Me	OEt	99	88
4-Me	OEt	OEt	90	
4-NO_2	Me	Me	91	
4-NO_2	Me	OEt	98	90
4-NO_2	OEt	OEt	88	
5-MeO	Me	OEt	98	91
4,5-Di-MeO	OEt	OEt	92	
3,4,5-Tri-MeO	Me	Me	84	
3,4,5-Tri-MeO	OEt	OEt	84	

An interesting series of reactions has been reported[785] to occur during the Robinson–Mannich annelation of cyclohexane-1,3-dione. Reaction of cyclohexane-1,3-dione with an equivalent amount of 1-diethylamino-3-butanone in refluxing benzene in the presence of pyridine, followed by acidification, affords β(2-methyl-7-oxo-3,4,4a,5,6,7-hexahydronaphthalene-1)propanoic acid in 45–50% yield (equation 288). However, when two equivalents of 1-diethylamino-3-butanone are used, the yield of the substituted propanoic acid is increased to 90–95%. This same



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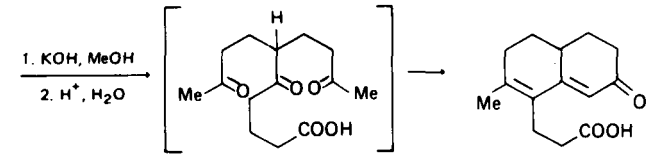
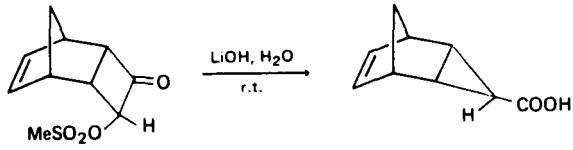


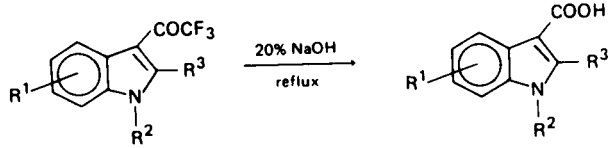
high yield of product is realized if the bis-adduct intermediate is hydrolysed via alkaline cleavage or by simply refluxing with diethylamine in benzene. Surprisingly, when annelation of cyclohexane-1,3-dione was carried out with butenone in the presence of Triton-B a different acid, β-(2-methyl-6-oxocyclohexene-1)propanoic acid, was obtained[785].

Aqueous lithium hydroxide at room temperature has been used to cleave the tricyclomethanesulphonic acid ester shown in equation (289) to afford[786] *endo-syn*-tricyclo[3.2.1.$0^{2,4}$]oct-6-en-3-carboxylic acid in 68% yield, formed by a four-carbon to three-carbon ring contraction. A 10% yield of the corresponding *endo-anti* carboxylic acid was also obtained.



(289)

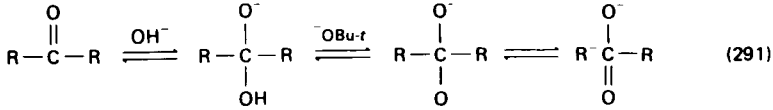
Hydroxy bases such as sodium hydroxide have also been used in the heterocycle field to cleave substituted 3-indolytrifluoromethyl ketones to substituted indol-3-carboxylic acids (equation 290)[787,788].



(290)

Since the original work of Gassman and coworkers[789,790] has been published, the cleavage of non-enolizable ketones with strong bases has received considerable attention[791-804]. Unlike the Haller–Bauer reaction[805], which involves the cleavage of ketones by sodium amide in refluxing benzene, toluene or xylene and yields amide and hydrocarbon moieties as products, the procedure of Gassman, which utilizes a 10 : 3 ratio of potassium *t*-butoxide–water mixture in aprotic solvents, such as ether (solvent of choice), dimethyl sulphoxide, glyme, hexamethylphosphoramide or hexane, affords carboxylic acids as products after only a few hours reaction time at room temperature. In addition, the stereochemistry of these reactions is such[790] that the acid function undergoes only a small amount of epimerization. The mechanism of cleavage of non-enolizable ketones with this

reagent mixture has been thoroughly investigated[790] and appears to involve initial addition of hydroxide ion to the carbonyl group followed by *t*-butoxide abstraction of a proton and cleavage of the resulting dianion (equation 291).

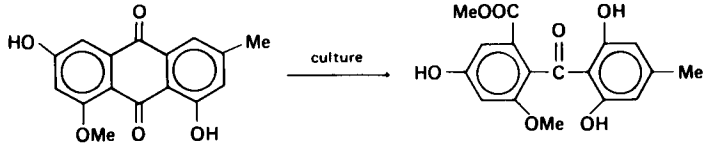


(291)

The extent to which this reaction has found synthetic usefulness for non-enolizable as well as for certain enolizable ketones, can be seen from the results in Table 41 which have been published on a wide range of systems by a variety of authors. A recent observation[806], which may be explained by a similar mechanism as that proposed by Gassman, is the conversion of benzophenone to benzoic acid using potassium hydride in THF–water solutions.

Hoffman and Cram[807,808] have published a rather complete study of the stereochemical reaction course of the base-catalysed cleavage of optically pure (+)-(*R*)-2-methyl-2-phenylcyclopentanone, and have found that in a variety of solvents (+)-(*S*)-5-phenylhexanoic acid was formed in 6–43% yield, with varying amounts of retention of configuration. Thus, in *t*-butyl alcohol–potassium *t*-butoxide about 61% net retention was observed, in dimethyl sulphoxide–*t*-butyl alcohol–potassium *t*-butoxide about 1% net retention and in diethylene glycol–potassium diethylene glycoxide approximately 27% net retention. To help establish the mechanism proposed[808] cleavage of (+)-(*R*)-5,5-dideuterio-2-methyl-2-phenyl-cyclopentanone in *t*-butyl alcohol–*O*-d-potassium *t*-butoxide was also investigated. This reaction gave the same hexanoic acid product with 62% net retention but which contained only 71% of one atom of deuterium at the methine carbon indicating that the carbanion intermediate was probably 'captured' by protons donated by the methyl groups of the medium.

A very interesting biodegradation of questin has been reported[809] in which the addition of questin to a 48-hour shake-flask culture of *Aspergillus terreus* (chlorine-free, Czapek–Dox medium), followed by further culture growth at 25°C for 25 hours, afforded sulochrin (equation 292). Using ^{14}C-labelled questin helped to



(292)

establish the mechanism for this biodegradative ketone cleavage, which appears to involve formation of the benzophenone from two distinct units each separately derived from acetate and malonate. The same transformation using *penicillium frequentans* has also been reported[810].

3. Of miscellaneous functional groups

Although ethers and ketones have been the two most common classes of compounds cleaved to produce acids and esters, other functional groups have also been reported to lead to acids under various cleavage conditions. Steroid alcohols have undergone fusion with potassium hydroxide[811] to afford acids, while pyrolysis of ethyl acrylate at 590°C has been reported[812] to lead to a 68–75% yield of acrylic acid.

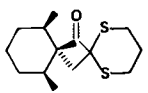
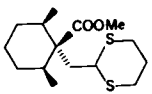
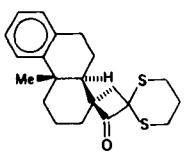
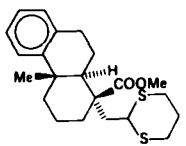
TABLE 41. Cleavage of non-enolizable and enolizable ketones

Starting ketone	System[a]	Product	Yield (%)	Reference
Nortricyclanone	A	*cis*- and *trans*-Bicyclo[3.1.0]hexane-3-carboxylic acid	65	789
Benzophenone	Varied	Benzoic acid	75–91	790–793
7-Ketonorbornene	A	Cyclohexene-4-carboxylic-acid + cyclohexene-1-carboxylic acid	32 18	790
Dehydronorcamphor	A	Cyclopentene-4-acetic acid	80	790
Camphenilone	A	Camphoceenic acid	9	790
Dehydronorcamphor	B	Cyclopentene-4-acetic acid	19	794
Fenchone	C	No cleavage		790
Fluorenone	C	Biphenyl-2-carboxylic acid	90	790, 792
Phenyl triphenylmethyl ketone	A	Benzoic acid	100	790
Xanthone	C	2-Phenoxybenzoic acid	64	792
2-Chlorobenzophenone	C	Benzoic acid + 2-chlorobenzoic acid	92 90	792
3-Chlorobenzophenone	C	Benzoic acid + 3-chlorobenzoic acid	93 91	792
4-Chlorobenzophenone	C	Benzoic acid + 4-chlorobenzoic acid	79 21	792
2-Carboxybenzophenone	C	Benzoic acid + phthalic acid	90	792
4-Carboxybenzophenone	C	Benzoic acid + terephthalic acid	85	792
4-Phenylbenzophenone	C	Benzoic acid + 4-phenylbenzoic acid	92	792
2-Methylbenzophenone	C	Benzoic acid + 2-methylbenzoic acid	59	792
3-Methylbenzophenone	C	Benzoic acid + 3-methylbenzoic acid	18 90	792
4-Methylbenzophenone	C	Benzoic acid + 4-methylbenzoic acid	73	792
2-Methoxybenzophenone	C	Benzoic acid + 2-methoxybenzoic acid	92 99	792
3-Methoxybenzophenone	C	Benzoic acid + 3-methoxybenzoic acid	90	792
4-Methoxybenzophenone	C	Benzoic acid + 4-methoxybenzoic acid	55	792
2-Chloro-4′-phenylbenzophenone	C	Biphenyl-4-carboxylic acid	91	795
2-Chloro-3′,4′-dimethylbenzophenone	C	3,4-Dimethylbenzoic acid	77	795

TABLE 41—*continued*

Starting ketone	System[a]	Product	Yield (%)	Reference
2-Chloro-2′,4′,6′-trimethylbenzophenone	C	2,4,6-Trimethylbenzoic acid	76	795
2-Chloro-3′,4′-dimethoxybenzophenone	C	3,4-Dimethoxybenzoic acid	85	795
2-Chloro-2′,4′-dimethoxybenzophenone	C	2,4-Dimethoxybenzoic acid	69	795
2-(2-Chlorobenzoyl)thiophen	C	Thiophen-2-carboxylic acid	–	795
2-(2,6-Dichlorobenzoyl)thiophen	C	Thiophen-2-carboxylic acid	72	795
9,10-Anthraquinone	D	Benzoic acid +	78	796
		phthalic acid	20	
Tetracen-5,12-quinone	D	Benzoic acid +	52	796
		β-naphthalenecarboxylic acid	42	
Dibenz[a,c]anthraquinone	D	Benzoic acid +	17	796
		phthalic acid +	51	
		9-phenanthrenecarboxylic acid	16	
Tetrabenz[a,c;h,j] anthraquinone-9-10	D	9-Phenanthrenecarboxylic acid +	44	796
		9,10-phenanthrenedicarboxylic acid	4	
9,10-Anthraquinone-β-carboxylic acid	D	Benzoic acid +	35	796
		phthalic acid +	16	
		iso- and terephthalic acid +	39	
		trimellitic acid	17	
Anthranthrone	D	1,1′-Dinaphthyl-2,2′-dicarboxylic acid +	4	796
		1,1′-dinaphthyl-8,8′-dicarboxylic acid	4	
1,2-Dibenzoylbenzene	E	Benzoic acid +	99	791
		phthalic acid	1	
1,3-Dibenzoylbenzene	E	Benzoic acid +	99	791
		isophthalic acid	1	
1,4-Dibenzoylbenzene	E	Benzoic acid +	99	791
		terephthalic acid	1	
4-Benzoylbiphenyl	E	Benzoic acid	50	791
1-Benzoylnaphthalene	E	Benzoic acid +	92	791
		α-naphthoic acid	8	
2-Benzoylnaphthalene	E	Benzoic acid +	91	791
		β-naphthoic acid	9	
6-Benzoylchrysene	E	Benzoic acid	45	791
1-Benzoylpyrene	E	Benzoic acid	40	791
1,3,6,8-Tetrabenzoylpyrene	E	Benzoic acid	84	791
1-(Naphthoyl-1)naphthalene	E	α-Naphthoic acid	50	791
2-(Naphthoyl-1)naphthalene	E	α-Naphthoic acid +	22	791
		β-naphthoic acid	29	
1-(Naphthoyl-1)pyrene	E	α-Naphthoic acid	44	791

TABLE 41 – *continued*

Starting ketone	System[a]	Product	Yield (%)	Reference
2,6-Di(naphthoyl-1)-naphthalene	E	2,6-Naphthalene dicarboxylic acid + α-naphthoic acid + β-naphthoic acid	45 3 1	791
Pivalophenone	E	Pivalic acid	50	791
Acetophenone	E	Benzoic acid	60	791
(2-Chlorobenzyl)ferrocene	C	(2-Carboxy)ferrocene	98	797
(2-Chlorobenzoyl)cyclopentadienylmanganese tricarbonyl	C	(2-Carboxy)cyclopentadienylmanganese tricarbonyl	87	797
2,3-Dihydro-1-benzoxepin-5-on-4-spirocyclopentane	C	Salicylic acid	89	798
2,2-(Propane-1,3-dithio)cyclohexanone	F or G	6,6-(Propane-1,3-dithio)hexanoic acid	93	799–801
2,2-(Propane-1,3-dithio)cycloheptanone	F or G	7,7-(Propane-1,3-dithio)heptanoic acid	95	799–801
2,2-(Propane-1,3-dithio)cyclooctanone	F or G	8,8-(Propane-1,3-dithio)octanoic acid	89	799–801
2,2-(Propane-1,3-dithio)-4-cyclohepten-1-one	F or G	(*Z*)-7,7-(Propane-1,3-dithio)-4-heptanoic acid	93	799–801
3,3-(Propane-1,3-dithio)-10-methoxymethyl-*trans*-2-decalone	F or G	1-[2,2-(Propane-1,3-dithio)ethyl]-*cis*-1-methoxymethylcyclohex-2-yl acetic acid	92	799–801
3,3-(Propane-1,3-dithio)-1,1-dimethyl-*trans*-2-decalone	F or G	No reaction	–	799–801
3,3-(Propane-1,3-dithio)-10-methyl-9-decen-2-one	F or G	No cleavage products	–	799–801
2-Thiophenylcyclohexanone	G	No reaction	–	801
2-Methyl-2-thiophenylcyclohexanone	G	No reaction	–	801
2,2-Bis(thiophenyl)cyclohexanone	G	6,6-Bis-thiophenylhexanoic acid	66	801
2,2-Dibromo-4-methyl-4-hexylcyclobutanone	H	Methyl-2-(2,2-dibromoethyl)-2-methyloctanoate	90	802
2,2-Dibromo-1-cyclobutanone-4-spirocyclohexane	H	1-(2,2-Dibromoethyl)-1-carbomethoxycyclohexane	97	802
2,2-(Propane-1,3-dithio)cyclobutanone-4-spiro(1-tetralone)	H	1-[2,2-(Propane-1,3-dithio)]ethyl-1-carbomethoxytetralone	60	803
2,2-(Propane-1,3-dithio)-4-(4-cyclohexenyl)cyclobutanone	I	2-(4-Cyclohexenyl)-4,4-(propane-1,3-dithio)butanoic acid	–	803
	H		–	803
	H		100	803

[a] A = KOBu-*t* + DMSO + H_2O, B = KOBu-*t* + *t*-BuOH, C = KOBu-*t* + glyme + H_2O, D = KOBu-*t* + dioxane + H_2O, E = KOBu-*t* + anisol + H_2O, F = NaOBu-*t* + NaOH + *t*-BuOH + ether, G = KOH + *t*-BuOH + H_2O, H = NaOMe + MeOH and I = NaOH + H_2O.

I. Acids by Rearrangements

In addition to the well-known rearrangement reactions a few novel and interesting rearrangements have been used to prepare acids and esters. This section will include a discussion of all types of rearrangements which have been used to prepare acids and/or esters.

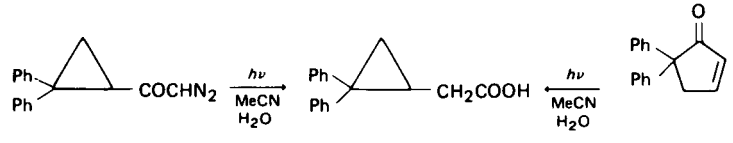
1. *Arndt–Eistert and Wolff Rearrangements*

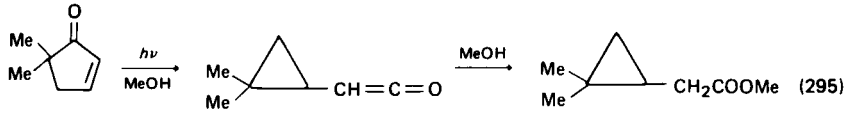
This rearrangement, which has been reviewed several times, beginning in 1941 by Eistert[813,814] by Bachmann and Struve[815] in 1942, by Eistert[816] again in 1948 and in 1964 by Weygand and Bestmann[817], involves the transformation of a carboxylic acid into its next higher homologue via a diazo ketone intermediate. The Wolff rearrangement, which accompanies the decomposition of the diazo ketone intermediate, is an integral step in any overall Arndt–Eistert synthesis.

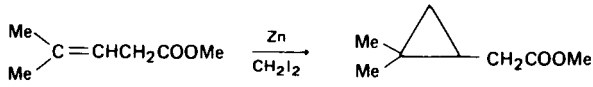
Several methods have been reported to prepare the intermediate diazo ketone required for this rearrangement, the most common method being treatment of an acid chloride with diazomethane or a substituted diazomethane, as shown in equation (293) for the preparation of 2-phenylpropionic acid[818]. A similarly

$$\mathrm{PhCOCl} \xrightarrow[\text{2. } Ag_2O,\ PhNH_2\text{; 3. acid hydrolysis}]{\text{1. } MeCHN_2,\ \text{ether}} \mathrm{PhCHMeCOOH} \qquad (293)$$

prepared diazo ketone was used in the preparation of 2,2-diphenylcyclopropaneacetic acid[819] via a photochemical Wolff rearrangement. This acid was also prepared[819] by photoisomerization of 5,5-diphenylcyclopentenone (equation 294). Photoisomerization of 5,5-dimethylcyclopent-2-enone[819] in the presence of methanol afforded the methyl ester of 2,2-dimethylcyclopropaneacetic acid (equation 295). The photochemical preparation of both the diphenyl-substituted acid and the dimethyl-substituted ester can be viewed as proceeding via a ketene in a reverse of the general vinylcyclopropane to cyclopentene rearrangement. Independent synthesis[819] of the dimethyl-substituted ester was accomplished by treatment of the methyl ester of 4-methyl-3-pentenoic acid with zinc and methylene iodide (equation 296).

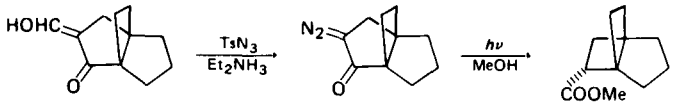






Another method used to prepare the required intermediate diazo ketone is illustrated by the reaction of 3-hydroxymethylene-2-oxo[3.3.2]propellane

(equation 297)[820,821] or 3-hydroxymethylene-2-oxo[4.2.2]propellane (equation 298)[820,821] with tosyl azide and diethylamine. These resultant diazo ketones were observed[821] to undergo ring-contraction via a photochemical Wolff rearrangement in methanol to give 65% yield of a mixture of epimeric 2-carboxy[3.2.2]propellane monomethyl esters or in aqueous dioxane to give 2-carboxy[3.2.2]propellane in 63% yield, respectively.



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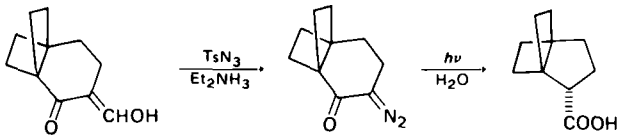
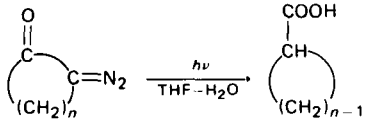


(298)

Similar ring-contractions have also been observed by Regitz and Ruter[822] upon photolysis of α-diazocyclic ketones in aqueous tetrahydrofuran (THF), producing cyclic acids (equations 299 and 300).



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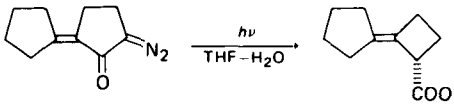
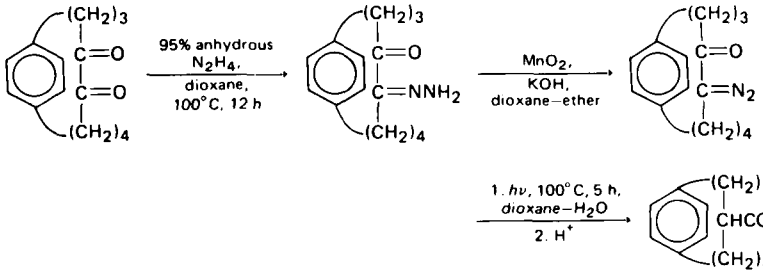


(300)

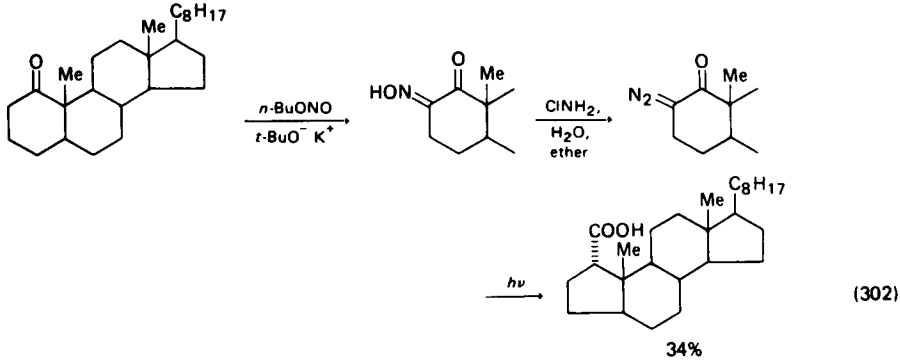
Diazo ketones of paracyclophanes have also been observed[823] to undergo ring-contractions during photochemical Wolff rearrangements to produce carboxylic acids, albeit in 25% yield. In this case[823] the required diazo ketone was prepared by base-catalysed manganese dioxide oxidation of 4,5-diketo-[9]-paracyclophane monohydrazone (equation 301).



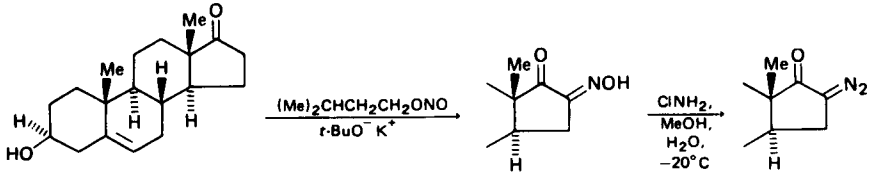
(301)

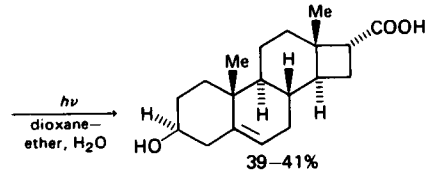
Ring-contractions producing carboxylic acids have also been reported in more complicated steroid systems. In each case the required diazo ketone has been

produced from an intermediate oxime by reaction with chloramine followed by a photochemical Wolff rearrangement (equations 302–304)[824-826].

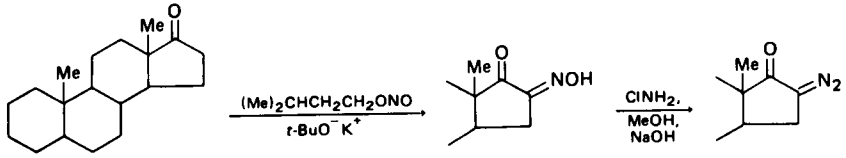


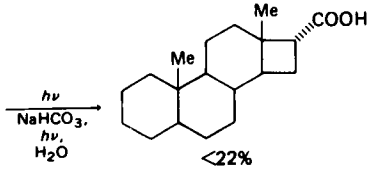
34% (302)





39–41% (303)

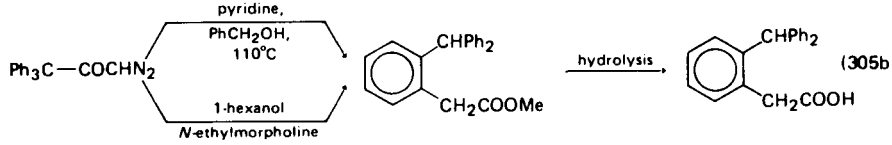




<22% (304)

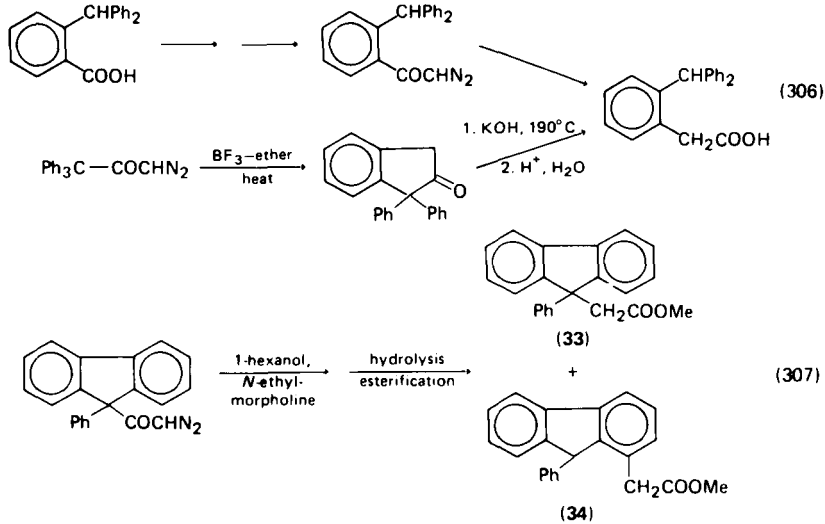
Even with the use of improved procedures[827-829] for the Wolff rearrangement of the intermediate diazo ketones, rearrangements have been reported[830] which do not proceed as expected but give abnormal acid derivatives which are isomeric with the expected product. Such a result was observed[830] upon heating triphenylacetyldiazomethane obtained by reaction of triphenylacetyl chloride with diazomethane (equation 305). Establishment of the structure of this product was accomplished by

$$Ph_3C{-}COCl + CH_2N_2 \longrightarrow Ph_3C{-}COCHN_2 \quad (305a)$$

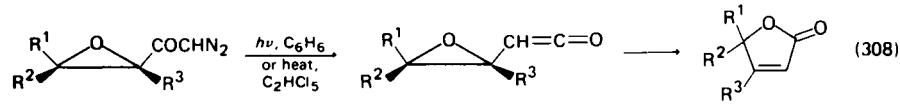


(305b)

two different independent syntheses[830], starting from triphenylmethane-*o*-carboxylic acid and 1,1-diphenyl-2-indanone, respectively (equation 306). In an attempt[830] to prove that this product was obtained because of steric interference with the normal Wolff rearrangement, 9-phenylflourene-9-carboxyldiazomethane was treated under similar conditions, to afford a 2 : 1 ratio of normal rearranged ester (33) to abnormal rearranged ester (34) (equation 307).

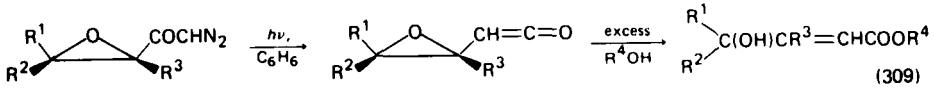


In addition to steric effects leading to abnormal products in the Wolff rearrangement, differences in reaction conditions can also lead to unexpected products during rearrangement as observed by Zwanenburg and coworkers[831]. Whereas photolysis of substituted α,β-epoxydiazomethyl ketones in benzene or simple reflux in pentachloroethane leads to intermediate epoxyketene formation and then to lactones (equation 308), photolysis in benzene in the presence of a ten-fold molar



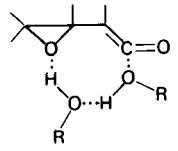
(308)

excess of methanol or ethanol leads to intermediate epoxyketene formation then to γ-hydroxy-α,β-unsaturated esters during rearrangement (equation 309)[831,832]. The interesting mechanism proposed[831] to explain these results involves spontaneous alcoholysis of the intermediate ketene via a cyclic transition state (35) involving



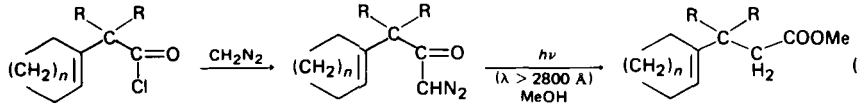
(309)

two associated alcohol molecules, one acting as a nucleophile on the ketene carbonyl carbon atom and the other serving as a proton source for the epoxide opening.

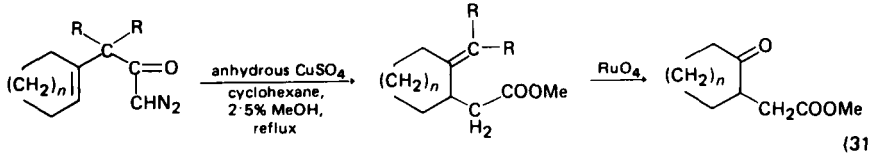


(35)

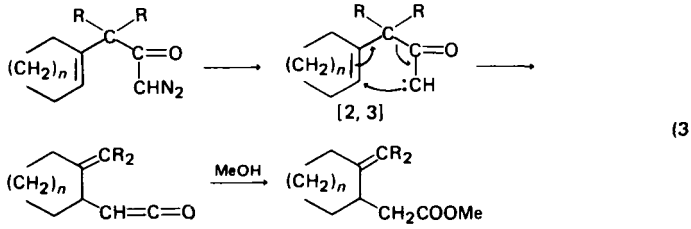
Other examples of unexpected products arising during the Wolff rearrangement are illustrated by the results of Smith[833], who found that photochemical rearrangement of unsaturated diazo ketones leads to the expected chain-lengthened ester (equation 310), while reflux in the presence of a copper sulphate catalyst generates, via skeletal rearrangement, a new γ,δ-unsaturated ester (equation 311). These products may be explained via a vinylogous Wolff-type [2,3]-sigmatropic rearrangement (equation 312).



(310)

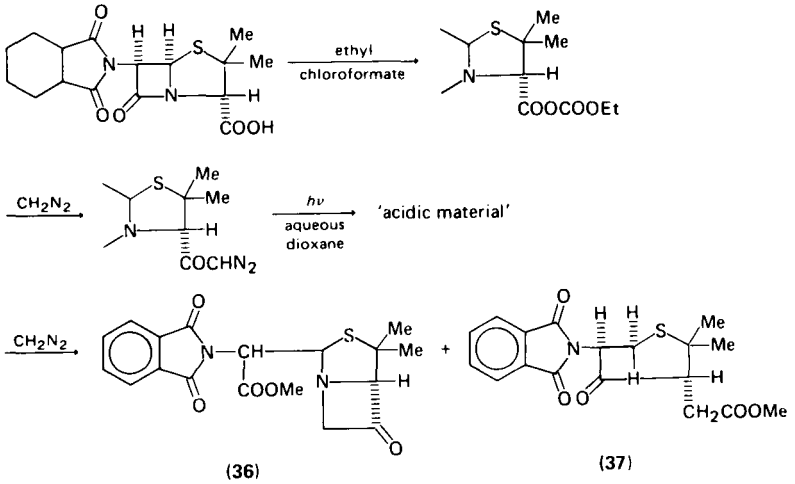


(311)



(312)

Arndt–Eistert reactions have also been applied to molecules related to penicillins such as the trimethylamine salt of 6-β-phthalimidopenicillanic acid[834]. In this case the intermediate diazo ketone, prepared by reaction of a mixed anhydride with diazomethane, upon photolysis afforded an 'acidic material', which upon esterification with diazomethane afforded 27% of methyl(α*R*, 2*R*, 5*S*)-α-(4,4-dimethyl-6-oxo-1-aza-3-thiabicyclo[3.2.0]hept-2-yl)-α-phthalimidoacetate (36) and 34% of methyl-6β-phthalimidohomopenicillanate (37).



(313)

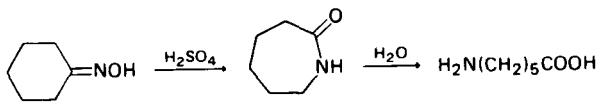
Application of the Arndt–Eistert reaction to 3-*o*-carborane derivatives[835] has shown that the Wolff rearrangement proceeds through boron–carbon bond cleavage and migration of the electron-rich 3-*o*-carboranyl group to the electron-deficient carbon centre to produce a carboranyl ketene, which upon hydrolysis affords 3-*o*-carborane-3-yl acetic acid. Production of the intermediate diazo ketone in these compounds was accomplished by treatment of the 3-*o*-carborane carboxylic acid chloride with diazomethane, while the standard silver oxide-catalysed decomposition of the diazo ketene was utilized to effect the Wolff rearrangement. Proof of structure of the 3-*o*-carborane-3-yl acetic acid obtained via this rearrangement was accomplished by an independent synthesis[835].

2. *Beckmann rearrangement*

This rearrangement, which degrades an acid into its next lower homologue, has been reviewed several times, first in 1934 by Franklin[836], then by Heldt and Donaruma[837] in 1960, and finally by Smith[838] in 1963.

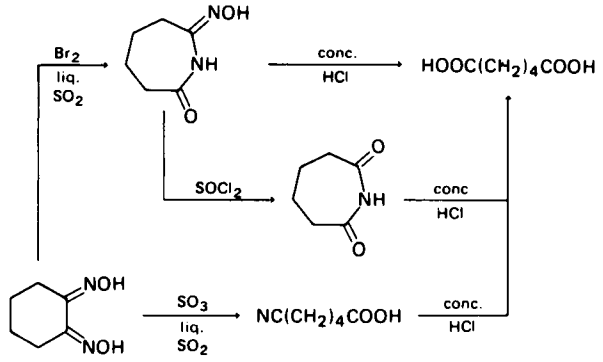
Although the most common Beckmann rearrangement involves treatment of an oxime with either concentrated sulphuric acid, phosphorus pentachloride and ether, hydrochloric acid–acetic acid–acetic anhydride mixtures or polyphosphoric acid[839] to produce a substituted amide, hydrolysis of the amide easily converts it into a carboxylic acid. Only those rearrangements which have been used to produce acids will be covered in this section.

A classic example of the use of the Beckmann rearrangement to prepare a carboxylic acid is that of Eck and Marvel[840] who treated cyclohexanone oxime with sulphuric acid to produce ε-caprolactam, which was then hydrolysed to ε-aminocaproic acid (equation 314).



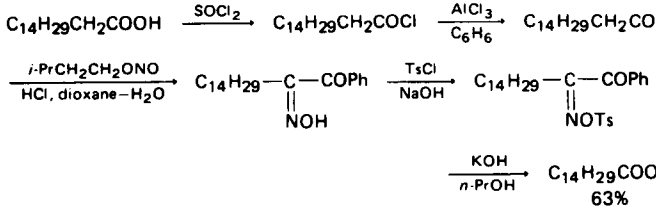
(314)

A similar approach was used[841] in the Beckmann rearrangement of 1,2-cyclohexanedione dioxime in liquid sulphur dioxide to produce adipic acid (equation 315).



(315)

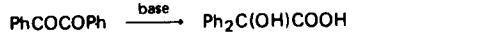
Dauben and coworkers[842] utilized the Beckmann rearrangement of an oxime tosylate to produce pentadecanoic acid from hexadecanoic acid via the intermediate formation of phenylpentadecyl ketone (equation 316).



(316)

3. *Benzilic acid rearrangement*

This rearrangement which has been most recently reviewed[843] in 1960, and which has been used essentially for the preparation of benzilic acid, involves the reaction of α-diketones with base causing rearrangement to the salts of α-hydroxy acids. For the preparation of benzilic acid itself from benzil (equation 317) a wide



(317)

variety of bases have been used, including concentrated aqueous potassium hydroxide[844], concentrated aqueous potassium hydroxide containing silver oxide[845], ethereal potassium hydroxide[846,847], and sodium amide in toluene[848]. The use of *o*-tolyllithium[849–851] and alkoxide ion has also been reported, and in the case of the alkoxide ion the benzilate ester is produced directly. With potassium *t*-butoxide–*t*-butyl alcohol in benzene the yield of *t*-butyl benzilate obtained (equation 318)[852] was 93%; however, with sodium methoxide the yield of methyl benzilate was considerably less[852]. Application of this rearrangement to aliphatic[853] and alicyclic[854] diketones as well as to substituted benzils[855,856] has also been reported.

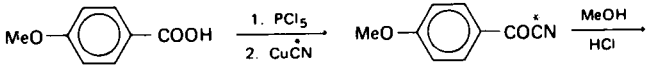
This rearrangement can also be applied to benzoin[857], which upon treatment with sodium bromate is first oxidized to benzil then converted to benzilic acid in

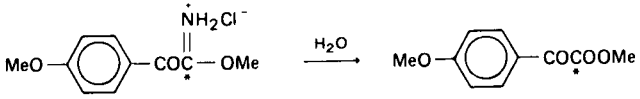
$$PhCOCOPh + K^{+}t\text{-}BuO^{-} \xrightarrow[C_6H_6]{t\text{-}BuOH} Ph_2C(OH)COOBu\text{-}t \qquad (318)$$

84–90% yield (equation 319), and to substituted benzoins such as α-*o*-tolylbenzoin[849–851].

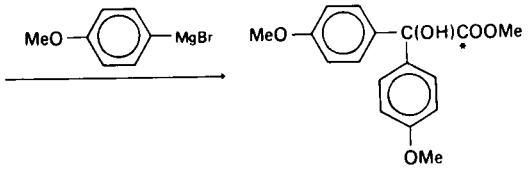
$$PhCH(OH)COPh + NaBrO_3 + NaOH \xrightarrow[H^{+}]{H_2O} Ph_2C(OH)COOH \qquad (319)$$

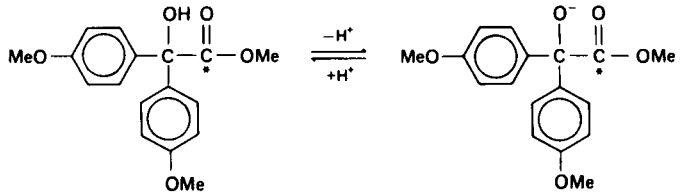
Recently, Eastham[858] has reported that the benzilic ester rearrangement is irreversible. This rearrangement, which is the reverse of the benzilic acid rearrangement, begins with an ester, which upon treatment with base was thought to convert the ester into a benzil. For his study of this rearrangement, Eastham[858] used as his model methyl anisilate-1-^{14}C, which he prepared in 22% yield from anisic acid via





(320)





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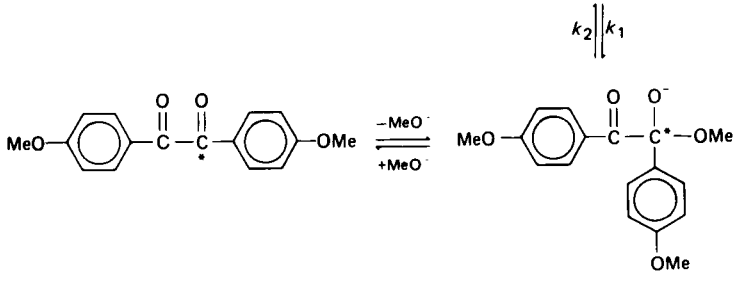


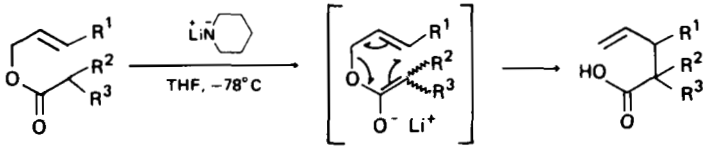
anisoyl cyanide-1-^{14}C, 4-methoxyphenylgloxylimino methyl ether-1-^{14}C hydrochloride and methyl-4-methoxyphenylglyoxylate-1-^{14}C (equation 320). This synthesis is novel because it is the first example of an imino ether hydrochloride being obtained from an aroyl cyanide.

The rearrangement Eastham proposed to study is shown in equation (321), using the methyl anisilate-1-^{14}C prepared above. In the scheme shown, k_2 is the step required for the benzilic acid rearrangement, while k_1 is the step under investigation. Treatment of methyl anisilate-1-^{14}C with potassium hydroxide followed by degradative saponification and oxidation with chromium trioxide, afforded only unlabelled dimethoxybenzophenone, a clear indication that no rearrangement had occurred.

4. Claisen rearrangement

This rearrangement which converts allyl aryl ethers, upon heating, to *o*-allylphenols has been reviewed by Tarbell[859] and Rhoads[860]. Although it is not common for the preparation of acids and/or esters, several reports have been made where acid or ester functions are present in the molecule during rearrangement, or where products from this rearrangement are converted into acids or esters, and our review of this rearrangement will be limited to such reports.

A typical example of the use of the Claisen rearrangement for the preparation of acids, which are then esterified using diazomethane, is the preparation of γ,δ-unsaturated acids from allyl esters (equation 322)[861]. In this study it was found that



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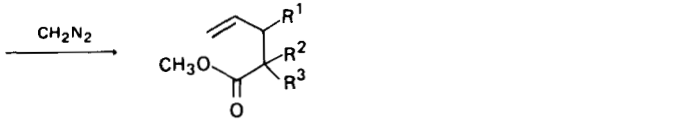

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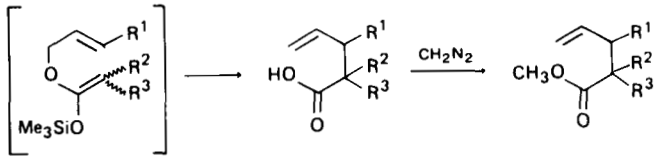
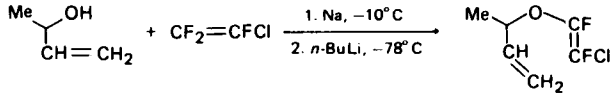


the allyl esters of tertiary and secondary acids rearranged rapidly at about room temperature as their lithium enolates, but that the acetates required quenching of these lithium enolates at −78°C with trimethylsilyl chloride before warming to effect good yields of rearranged acids (equation 323).

A similar Claisen rearrangement of trihalogenated analogues of allyl esters was reported by Normant and coworkers[862], who prepared the required difluorochlorovinyl allyl ethers by reaction of the sodium enolate of various 1-ene-2-ols with trifluorochloroethene. These products all rearranged at −35 to +25°C to afford γ,δ-unsaturated acid fluorides which were converted into the corresponding acids or esters by treatment with water or methanol, respectively (equations 324–328). The products can be rationalized on the basis of a [3,3]-sigmatropic Claisen-type rearrangement (equation 329).

A study of the stereoselectivity of the Claisen rearrangement of allyl siloxyvinyl ethers for the preparation of the Queen Butterfly pheromone has been recently reported by Katzenellenbogen and Christy[863]. Treatment of 2-bromopropene with



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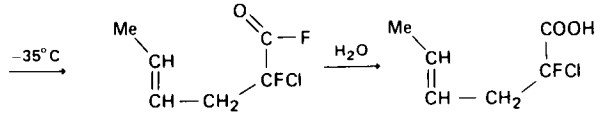

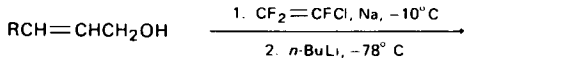

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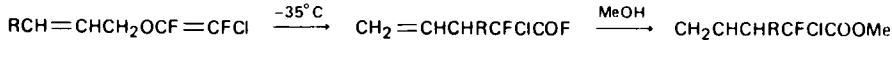

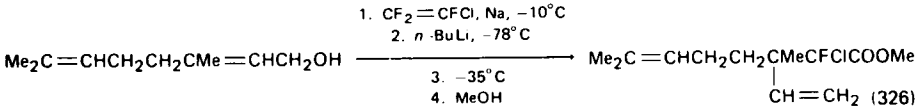

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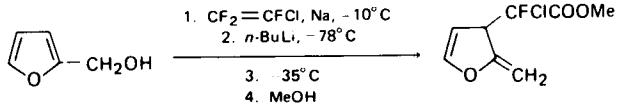

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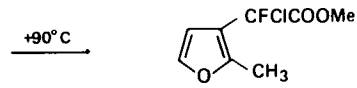
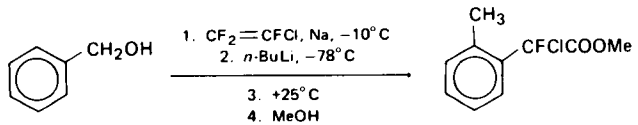
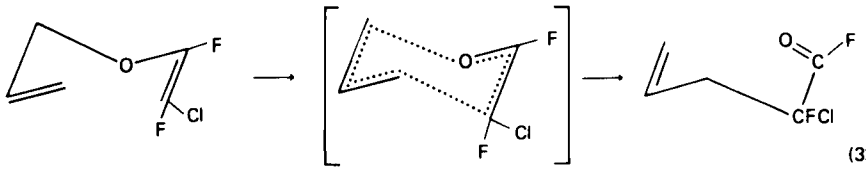




(328)



(329)

magnesium, followed by reaction of the resulting Grignard reagent with heptanal, afforded a 72% yield of 3-hydroxy-2-methyl-1-nonene which was converted into 3-acetoxy-2-methyl-1-nonene upon treatment with acetic anhydride in pyridine (equation 330). Derivatization of this product with isopropylcyclohexyl amine,

$$CH_3CBr{=}CH_2 \xrightarrow[\substack{I_2,\ N_2\\ 2.\ \text{heptanal}}]{1.\ Mg,\ THF,} n\text{-}C_6H_{13}CH(OH)CMe{=}CH_2 \quad (72\%)$$

$$\xrightarrow[\substack{\text{pyridine}\\ 40\ h,\ 25^\circ C}]{Ac_2O} n\text{-}C_6H_{13}CH(OAc)CMe{=}CH_2 \quad (92\%) \qquad (330)$$

n-butyllithium and trimethylsilyl chloride, afforded the corresponding trimethylsiloxyvinyl ether, which underwent the Claisen-type [3,3]-sigmatropic rearrangement in 53% yield and with a greater than 98% stereoselectivity, to give (*E*)-4-methyl-4-undecenoic acid, which was converted into its methyl ester by treatment with diazomethane (equation 331). Rearrangement of the *t*-butyldi-

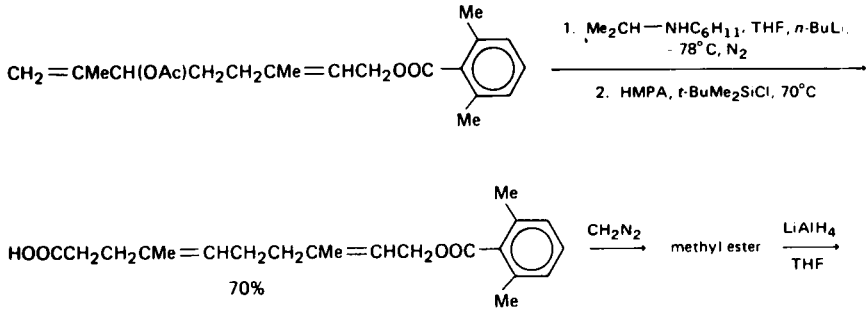
$$n\text{-}C_6H_{13}CH(OAc)CMe{=}CH_2 \xrightarrow[\substack{-78^\circ C,\ N_2\\ 2.\ Me_3SiCl,\ 70^\circ C}]{1.\ Me_2CH{-}NHC_6H_{11},\ THF,\ n\text{-}BuLi,}$$

$$n\text{-}C_6H_{13}CH{=}CMeCH_2CH_2COOH \xrightarrow{CH_2N_2} n\text{-}C_6H_{13}CH{=}CMeCH_2CH_2COOMe \qquad (331)$$

methylsiloxyvinyl ether derivative, prepared by treatment of 3-acetoxy-2-methyl-1-nonene with isopropylcyclohexyl amine, *n*-butyllithium and *t*-butyldimethylsilyl chloride, also afforded (*E*)-4-methyl-4-undecenoic acid in 80% yield, also with a very high degree of stereoselectivity. Application of this rearrangement to (*E*)-3-acetoxy-8-mesitoyloxy-2,6-dimethyl-1,6-octadiene prepared via a four-step synthesis from geraniol, afforded 70% of (*E,E*)-10-mesitoyloxy-4,8-dimethyl-4,8-decadienoic acid which, upon reduction and cleavage of the mesitoate, produced the pheromone (*E,E*)-3,7-dimethyl-2,6-decadiene-1,10-diol in 87% yield (equation 332). The intermediate acid was also converted into its methyl ester upon treatment with diazomethane.

The mechanism of this rearrangement (equation 333) again involves initial formation of the lithium enolate, which first undergoes *O*-silylation to afford the enol silyl ether and then undergoes the Claisen rearrangement.

Upon treatment of monoacylated 4-methylcyclohex-3-ene-1,2-diol with two moles of 1-methoxy-1-dimethylamino ethylene, Lythgoe and coworkers[864] observed two successive alkoxy exchanges followed by a modified Claisen-type rearrangement, where the shift of a double bond caused concomitant stereospecific transfer of two $-CH_2CONMe_2$ groups to the former allyl termini, affording, after hydrolysis of the amide group, 1-methylcyclohex-3-ene-1,2-diacetic acid in 44%



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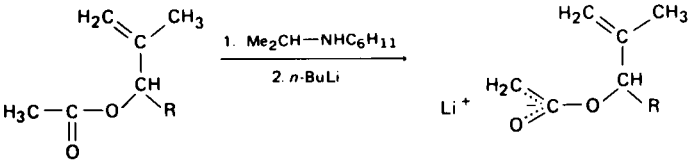

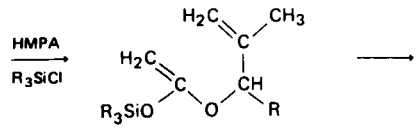

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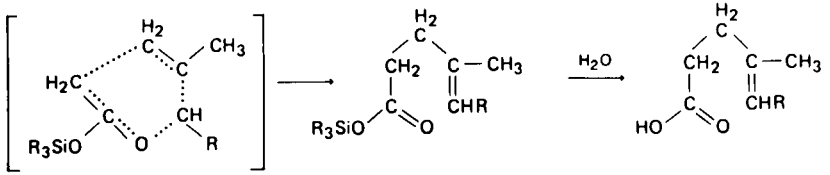
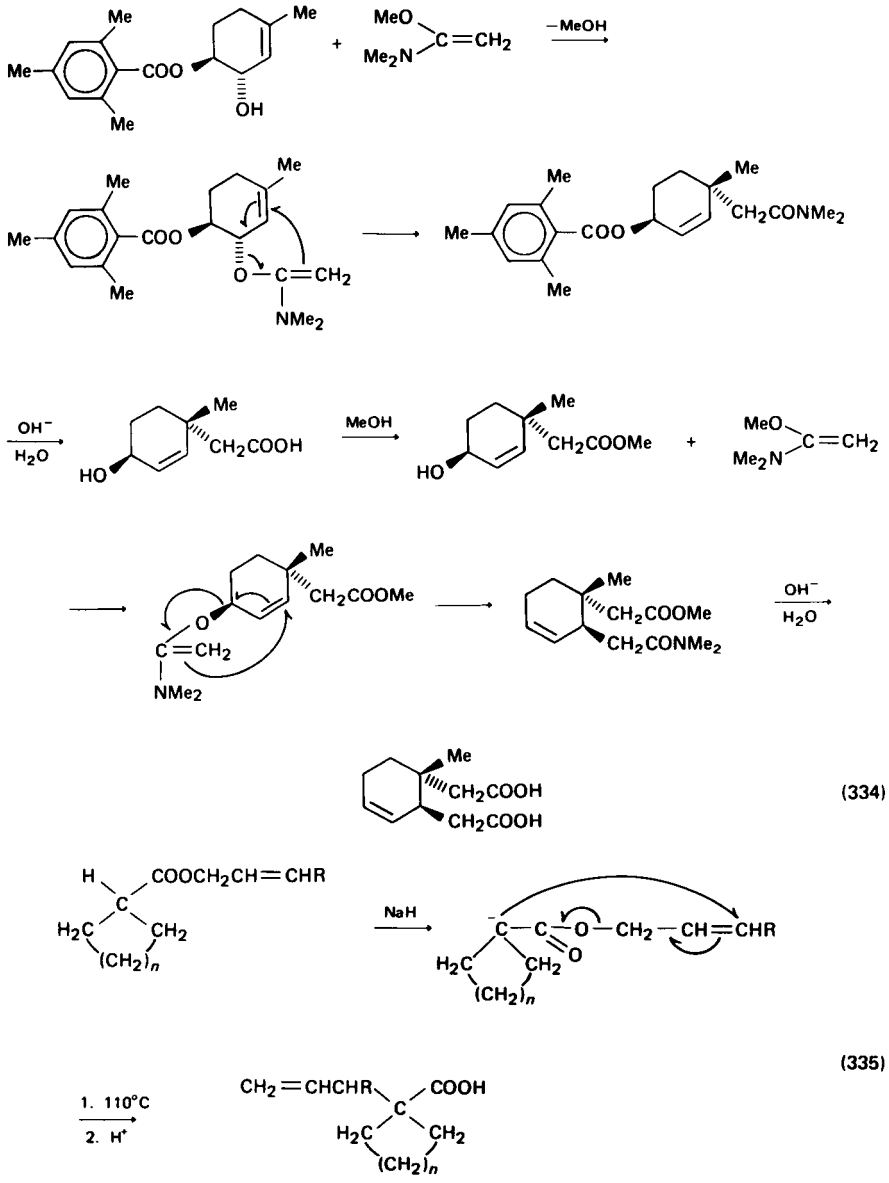


overall yield (equation 334). Additional examples of such rearrangements may be found in Section VII.C. This method, when applied to a mixed monoacetate, was shown[864] to be effective in allowing only the β,γ-unsaturated monoacetate to undergo two successive Claisen rearrangements, whereas the α,β-unsaturated monoacetate was recovered in the form of the diol after only one rearrangement (Scheme 6).

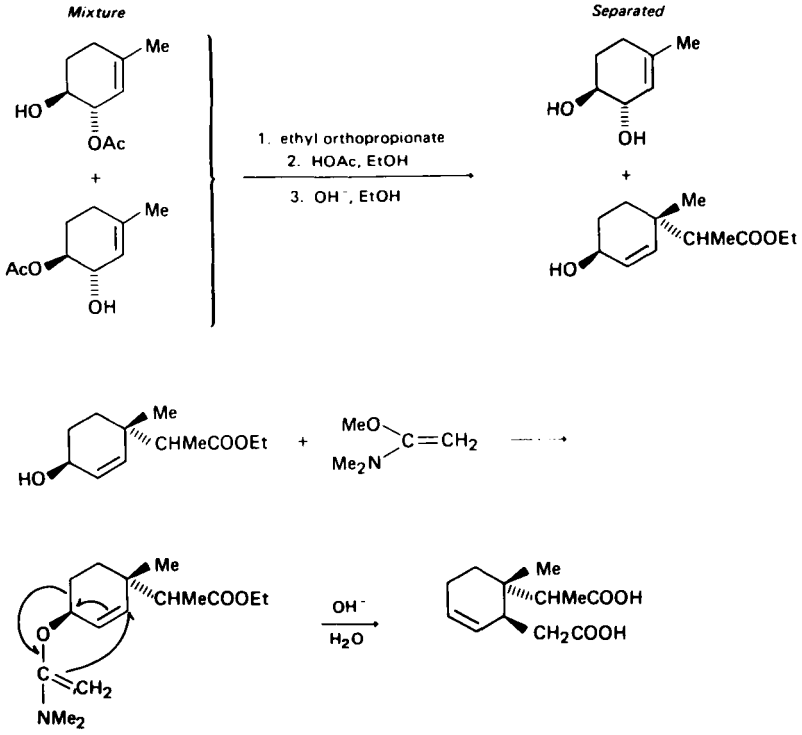
The ability of the anion derived from allylic esters of cycloalkanecarboxylic acids to undergo intramolecular allylation via a Claisen-type rearrangement has been shown by Arnold and Hoffman[865] to occur in about 40% yield. Allyl cyclopentane- and cyclohexanecarboxylates and cinnamyl cyclohexanecarboxylate were individually treated with sodium hydride to effect formation of the respective anions which upon heating at 110° for 24 hours, followed by acidification, afforded the corresponding acids (equation 335).



(334)

(335)

Abnormal Claisen rearrangements, that is, normal *ortho* Claisen rearrangement of a γ-alkylallylphenyl ether to an *o*-(α-alkylallyl)phenol followed by an isomerization of the side-chain of the phenol, have also been reported[866] in the literature. Since the mechanism of the secondary isomerization has been formulated as involving a cyclopropyldienone intermediate[866,867], Roberts and coworkers[868,869] reasoned that this mechanism should not be restricted to phenols,



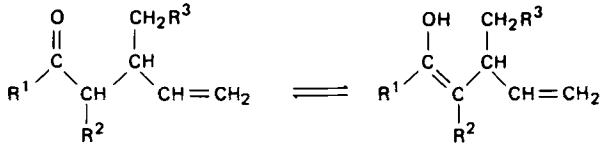
SCHEME 6.

but should be viewed as a general type of intramolecular rearrangement which could be utilized to convert one homoallylic carbonyl compound (38) to another (42) via the allylic enols 39 and 41 and the cyclopropyl carbonyl compound 40. These reports showed, not only that the sequence indicated in equation (336) occurs for a variety of substituted molecules, but also that it is reversible.

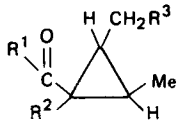
A new, synthetically useful, sigmatropic Reformatsky–Claisen rearrangement has also been reported[870], in which α-bromo esters derived from allylic and acetylenic alcohols are treated with zinc dust and undergo a [3,3]-sigmatropic rearrangement of the intermediate zinc enolate to afford γ,δ-unsaturated acids. Using this method α,α-dimethyl-α-allenic acid has been prepared in quantitative yields from 1-propynyl-3-(α-bromo-α-methylpropionate) (equation 337). The mechanism of this novel Claisen-type rearrangement is illustrated in equation (338) for the preparation of 2-methylhex-4-enoic acid from 1-butene-3-(α-bromopropionate).

5. Favorskii rearrangement

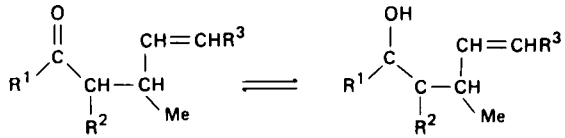
This rearrangement, which involves the reaction of α-chloro or bromo ketones with either alkoxide ion to produce rearranged esters, or with hydroxide ion to produce free acids (salts), has been reviewed at least three times by Jacquier[871] in 1950, by Tchoubar[872] in 1955, and, most recently, by Kende in 1960[873]. Although the normal Favorskii rearrangement involves the use of strong bases as



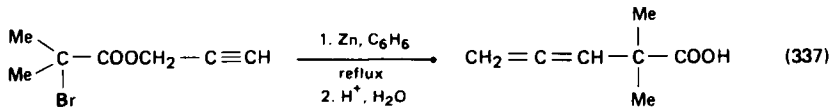
(38) (39)



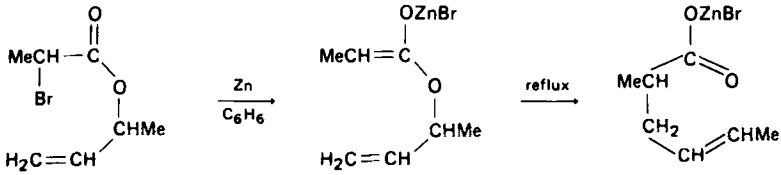
(40) (336)

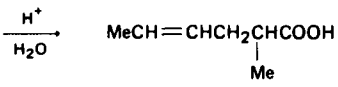


(42) (41)



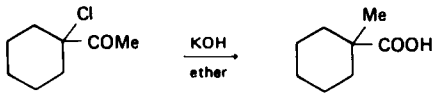
(337)





(338)

illustrated in equations (339)–(341) for the preparation of 1-methylcyclohexanecarboxylic acid[874], methyl cyclopentanecarboxylate[875] and long-chain fatty acids[876], mild bases have also been used. Sodium bicarbonate[877] has been used as the base in the preparation of *cis*-crotonic acid from 1,3-dibromo-2-butanone

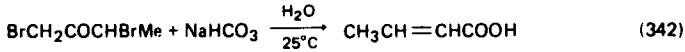


(339)

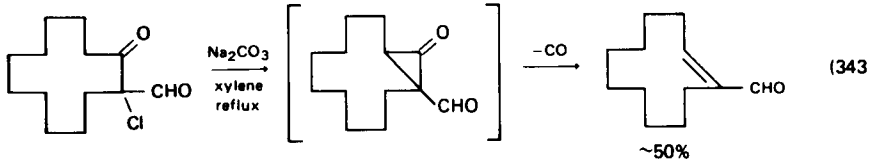
(340)

(341)

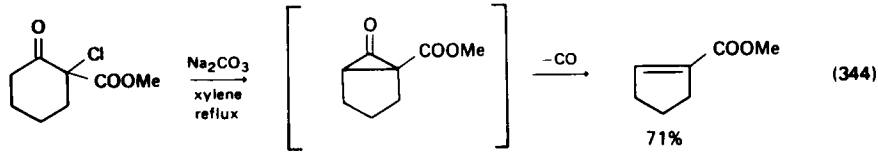
(equation 342), while sodium carbonate in hot xylene has been used to prepare cyclopentenones in the synthesis of methyl jasmonate and jasmone[878], cyclopentenone intermediates for the synthesis of prostaglandins[879,880], cycloundecene-1-carboxaldehyde (equation 343)[881], and 1-carbomethoxycyclopentane from 2-chloro-2-carbomethoxycyclohexanone (equation 344)[881].



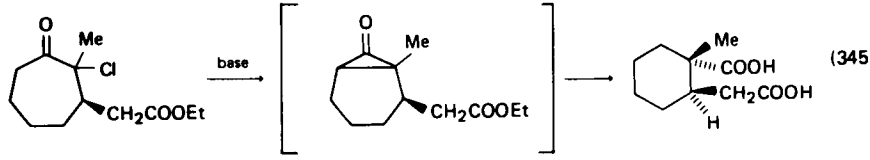
(342)



(343)



(344)

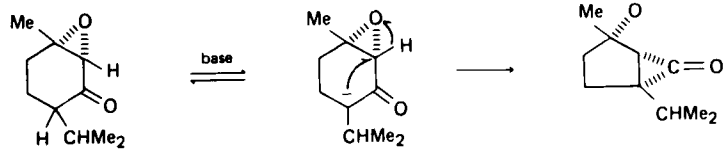


(345)

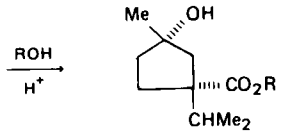
A study of the best conditions under which to run the Favorskii rearrangement, including the effect of the alkoxide types, their concentration and the resultant stereochemistry of the resulting products, has been made by Stork and Borowitz[882] for the preparation of *trans*-2-carboxycyclohexaneacetic acid (equation 345). Their findings showed the yield of product to decrease with the following order of alkoxide base used:

Benzyloxide ($C_6H_5CH_2O^-$) > ethoxide > methoxide > isopropoxide

The non-stereospecificity of the Favorskii rearrangement in the reaction of piperitone oxide (43) and isophorone oxide with sodium methoxide or potassium hydroxide in methanol or methanol–water mixtures has also been reported (equation 346)[883].

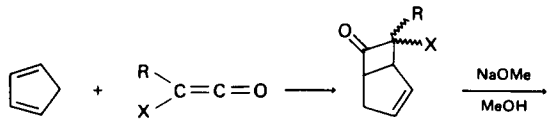


(43)

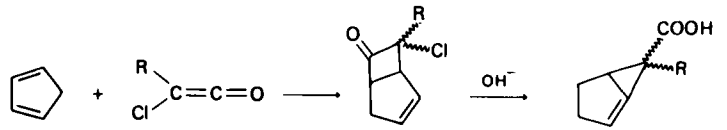


(346)

More recently, Favorskii-type rearrangements of haloketene olefin cycloadducts have appeared in the literature and a study of the stereospecificity of these rearrangements has also been reported. Thus, Brady and Hreble[884] have reported that rearrangement of a bicyclo[3.2.0]hept-2-en-6-one ring-system to the bicyclo-[3.1.0]hex-2-ene ring-system in the presence of sodium methoxide in refluxing methanol affords a product of unspecified stereochemistry (equation 347). In



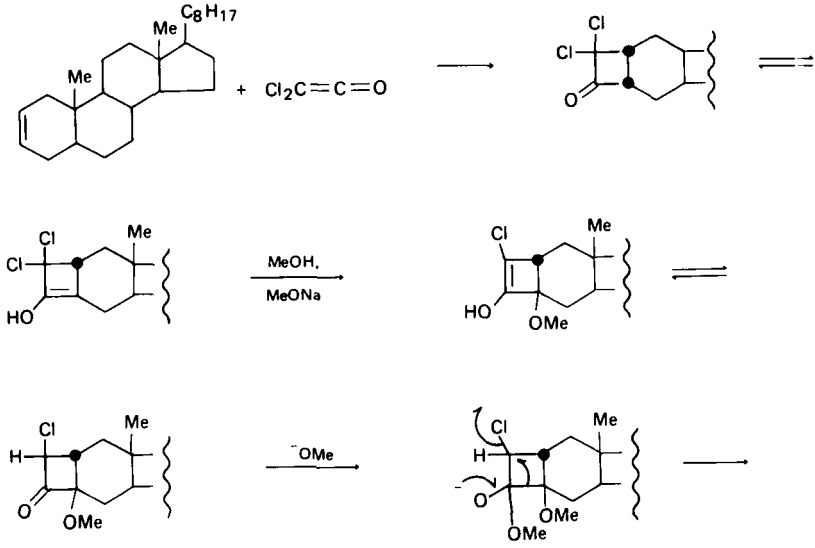
(347)

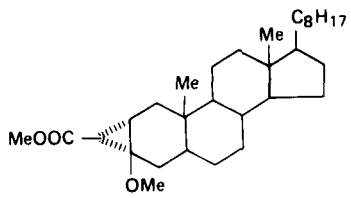


(348)

R = Me, Et, *i*-Pr
% = 97, 65, 0

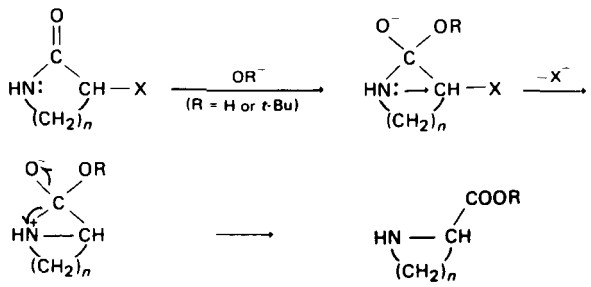
contrast, Harrison and coworkers[885,886] have reported a study of the same rearrangement using potassium hydroxide, which not only demonstrates that the *endo* acid is obtained from the *endo* haloketene olefin cycloadduct and the *exo* acid is obtained from the *exo* haloketene olefin cycloadduct, but that the proportion of *endo* haloketene olefin cycloadduct increases as the size of the alkyl group R on the ketene increases (equation 348). Fletcher and Hassner[887] has applied this rearrangement to the preparation of a 2 : 1 ratio of *endo* to *exo* bifunctional cyclopropane-containing steroids (equation 349).





(349)

endo: exo = 2:1

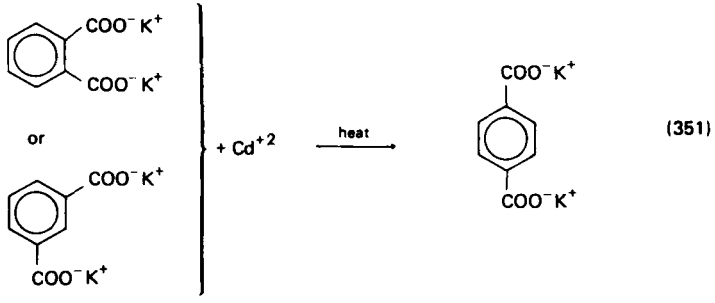


(350)

An extension of the Favorskii rearrangement to α-halogenated ω-amino lactams has also been reported[888]. In this case the initial lactam rearranges via a bicyclic aziridinone to an α-imino acid, affording a novel synthesis of medium ring-size cyclic α-imino acids homologous to proline. The reagent of choice for this rearrangement was found to be potassium *t*-butoxide in either *t*-butyl alcohol, tetrahydrofuran or dioxane, although sodium hydroxide in aqueous dioxane was also observed to afford product. The mechanism proposed is shown in equation (350).

6. Henkel reaction (Raecke process)

The Henkel reaction, which involves the thermal rearrangement or disproportionation of aromatic carboxylates of alkali metals to symmetrical aromatic dicarboxylates, has been reviewed[889]. This reaction is usually carried out between 200 and 500°C in an inert atmosphere and in the presence of catalytic quantities of cadmium salts, as exemplified[890] by the conversion of phthalic or isophthalic acid to terephthalic acid in 90–95% yield (equation 351), the rearrangement of salicylic acid to *p*-hydroxybenzoic acid in 70–80% yield (equation 352) and the conversion of 1,8-naphthalenedicarboxylic acid into 2,6-naphthalenedicarboxylic acid in 57–61% yield (equation 353)[891]. Similar results have been obtained[892] with 1- and 2-naphthoic acid, and naphthalene-1,3-, 2,3-, 1,6-, 1,8- and 2,7-dicarboxylic acids, all of which have been converted to 2,6-naphthalenedicarboxylic acid under a variety of conditions, using a variety of catalysts. The mechanism of this reaction has been studied by several investigators[892–895] and is believed to be intermolecular in nature.



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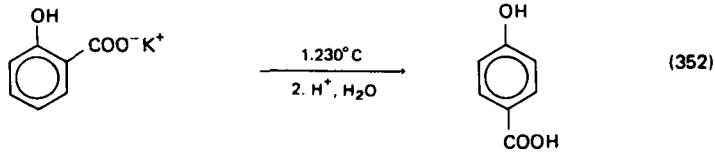

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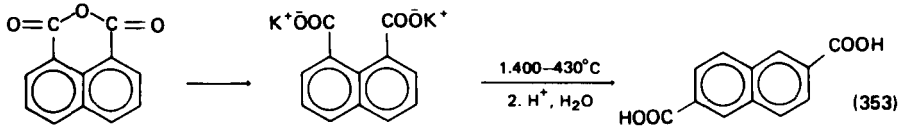
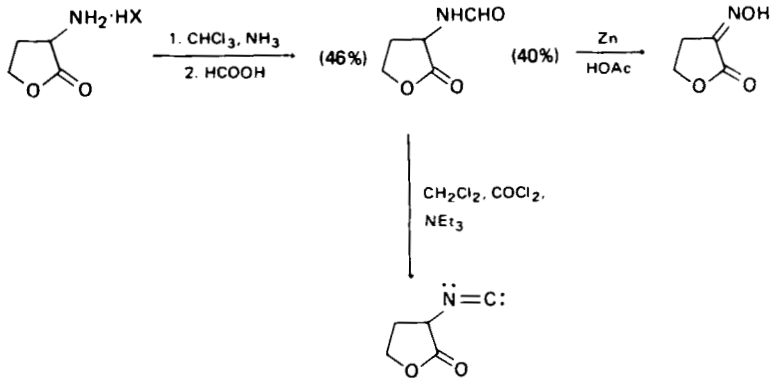


(353)

For additional information on this topic see the chapter on transcarboxylations by Ratuský in this volume.

7. *Isonitrile rearrangement*

Only one reference[896] appears in the current literature concerning the formation of an ester from an isonitrile, and this reaction involves the base-catalysed opening of the γ-lactone ring of α-isocyano-γ-butyrolactone to afford 35% yield of 4-carbethoxy-5,6-dihydro-4*H*-1,3-oxazine. The synthetic methods used for the preparation of α-isocyano-γ-butyrolactone and the mechanism of its base-catalysed ring-opening are shown in equations (354 and (355).



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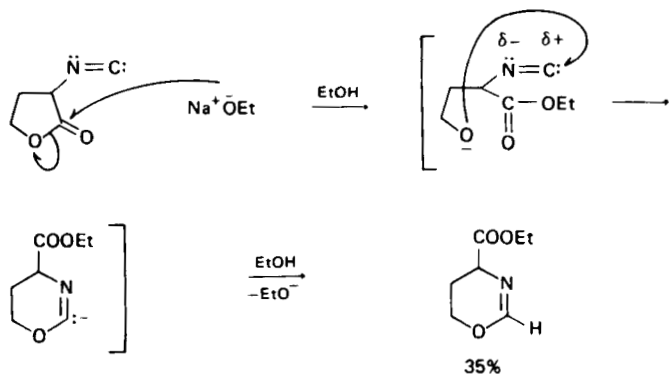
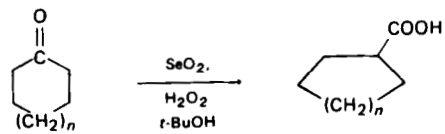


(355)

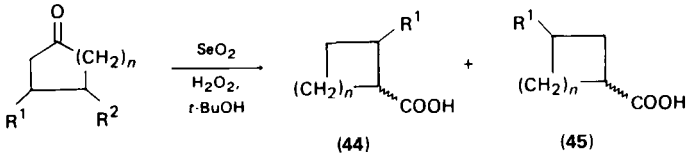
8. *Oxidative ring-contraction*

A variety of cyclic ketones have been treated with selenium dioxide–hydrogen peroxide mixtures to afford cyclic carboxylic acids containing one carbon less in the cycle (equation 356). These reactions all involve oxidative ring-contractions and



(356)

are not very effective since the yields are in the range of 20–40%[897,898] A study of alkyl-substituted cyclopentanone and cyclohexanone conversion to alkyl-substituted cyclobutanoic and cyclopentanoic acids has also been reported[899], in which the size of the alkyl group has been observed to affect the structure and stereochemistry of the resulting acids (equation 357). The mechanism for this rearrangement is not thoroughly understood.

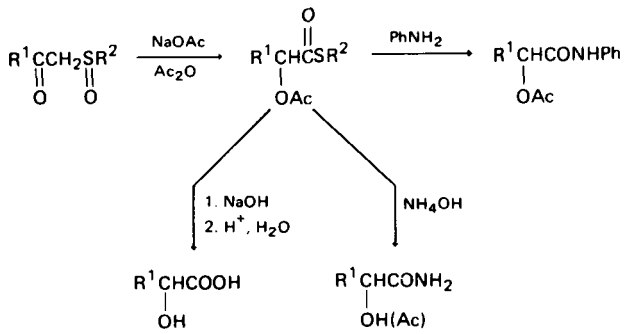


(357)

R¹	R²	n	Total yield (%)	44 (%)		45 (%)	
				cis	*trans*	*cis*	*trans*
Me	H	1	26	0	52	32	16
t-Bu	H	1	26	0	28	48	24
Me	H	2	25	11	25	36	28
H	Me	2	28	0	0	66	34
t-Bu	H	2	37	0	0	100	0
H	*t*-Bu	2	40	0	0	100	0

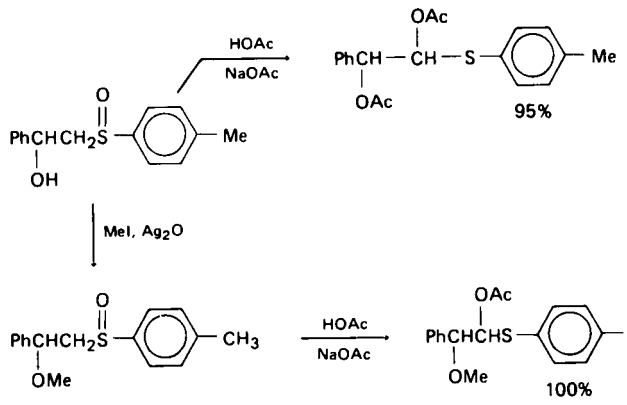
9. *Pummerer rearrangement*

This rearrangement is an intramolecular oxidation–reduction of sulphoxides, which upon treatment with acetate ion afford sulphides, with concomitant oxidation of the α-carbon. When applied to β-keto sulphoxides[900] this rearrangement affords α-acetoxy acid thio esters which can be hydrolysed to β-hydroxy acids, amides or substituted amides, depending upon which base is used for the hydrolysis (equation 358). When applied[901] to β-hydroxy sulphoxides such as 2-hydroxy-



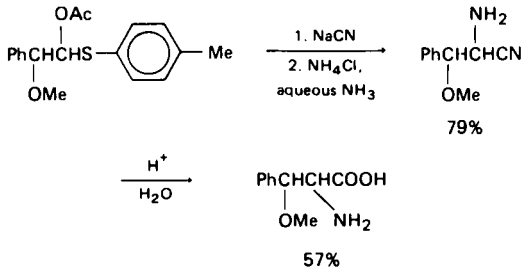
(358)

2-phenylethyl *p*-tolyl sulphoxide, a 95% yield of 1,2-diacetoxy-2-phenylethyl *p*-tolyl sulphide was obtained; however, if the β-hydroxy group is first methylated using methyl iodide and silver oxide, then the resultant 2-methoxy-2-phenylethyl *p*-tolyl sulphide is converted, in quantitative yield, to 1-acetoxy-2-methoxy-2-phenylethyl *p*-tolyl sulphide (equation 359). This product can be converted to



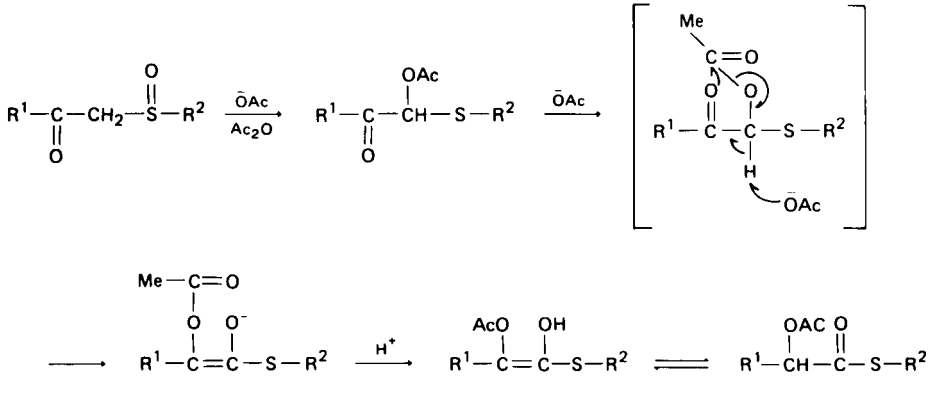
(359)

DL-*threo*-*O*-methylphenylserine in 57% yield via treatment with sodium cyanide, giving 2-amino-3-methoxy-3-phenylpropionitrile, followed by acid hydrolysis.



(360)

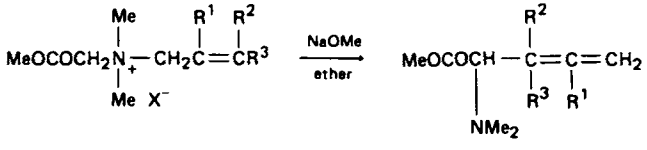
The mechanism[900] of this rearrangement is shown in equation (361) and is believed to involve initial formation of the α-acetate with reduction of the sulphoxide group followed by a base-catalysed intramolecular oxidation–reduction with concomitant acetyl transfer.



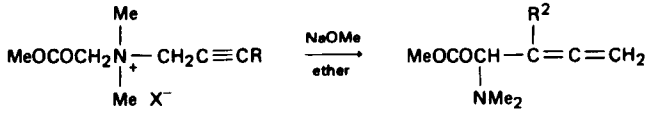
(361)

10. Stevens rearrangement

Two discussions of the Stevens rearrangement have appeared in the literature, the first by Zimmerman in 1963[902], and the second by Cram in 1965[903]. This rearrangement, which involves treatment of a quaternary ammonium salt containing an electron-withdrawing group on one of the carbons attached to the nitrogen with a strong base to produce a rearranged tertiary amine, has been used only once in the recent literature[904] for the preparation of amino substituted acids or esters. With the electron-withdrawing group attached to nitrogen being a carbalkoxymethyl group, substituted allyldimethyl ammonium halides upon treatment with sodium methoxide afforded 70–90% yield of γ,δ-unsaturated-α-dimethylamino-substituted esters (equation 362). Propargyl-substituted ammonium halides give rise to allenic esters (equation 363).



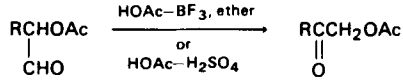
(362)



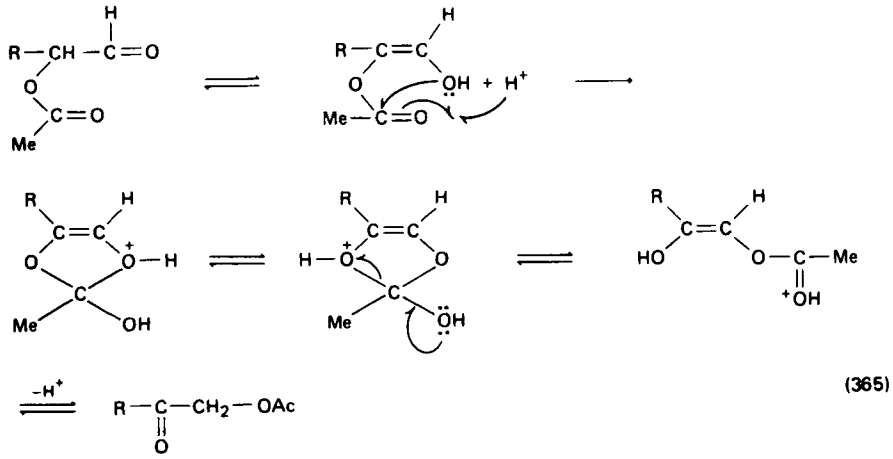
(363)

11. Miscellaneous rearrangements

A variety of miscellaneous rearrangements, which do not lend themselves to inclusion with the name rearrangements discussed above, but which lead to the



(364)



(365)

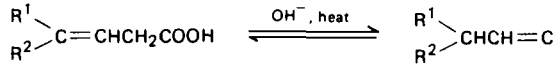
production of acids or esters, have also been reported in the literature. This section will attempt to discuss these rearrangements under the category of the catalyst which is used to effect the rearrangement.

a. Acid-catalysed rearrangements. Treatment of a variety of α-acetoxyl aldehydes with acetic acid–sulphuric acid mixtures or with acetic acid–boron trifluoride etherate mixtures has been reported[905] to produce > 90% yields of α-acetoxy ketones (equation 364). The isomeric ketones can be visualized as arising via the mechanism shown in equation (365).

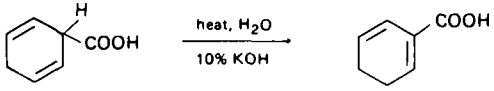
A considerably more involved mechanism (Scheme 7) has been proposed[906] for the rearrangement of tricyclic ketones, such as 1,5-dimethyl-6-methylenetricyclo [3.2.1.$0^{2,7}$]oct-3-en-8-one, in neat formic acid (99%), at room temperature upon standing for 8–72 hours without exclusion of air, to the previously unreported ring-polymethylated phenylacetic acids. The yields range from 96% for the parent compound ($R^1 = R^2 = R^3 = R^4 = H$) to 25% for the methylated case ($R^1 = R^2 = R^4 = H$, $R^3 = Me$).

b. Alkoxycarbonyl group rearrangement. Although this type of rearrangement has been observed in reactions already discussed, such as the benzilic acid and the Favorskii rearrangements, other examples have also been reported in Michael additions, sigmatropic rearrangements and solvolytic reactions, all of which lead to acids or esters. An excellent review on the migrations of alkoxycarbonyl groups has been written by Acheson[907] and the reader is referred to this review for more detailed information.

c. Base-catalysed rearrangements. The base-catalysed rearrangements which lead to acids or esters are of two kinds, isomerization reactions and hydrolysis reactions. The base-catalysed isomerization reactions consist of the treatment of β,γ-unsaturated acids, esters or amides with a base such as potassium hydroxide and, in some cases, heat, to effect isomerization to the α,β-conjugated isomer. The pre-1943 work in this area has been reviewed by Gilman[908]. Two more recent examples of this type of isomerization reaction, which have appeared in the literature, consist of the base-catalysed isomerization of γ,γ-disubstituted-β,γ-unsaturated butanoic acids[909] to γ,γ-disubstituted-α,β-unsaturated butanoic acids (equation 366), and the isomerization of 1,4-dihydrobenzoic acid to 3,4-dihydrobenzoic acid in 80% yield (equation 367)[910].

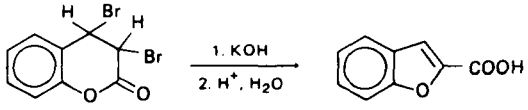


(366)

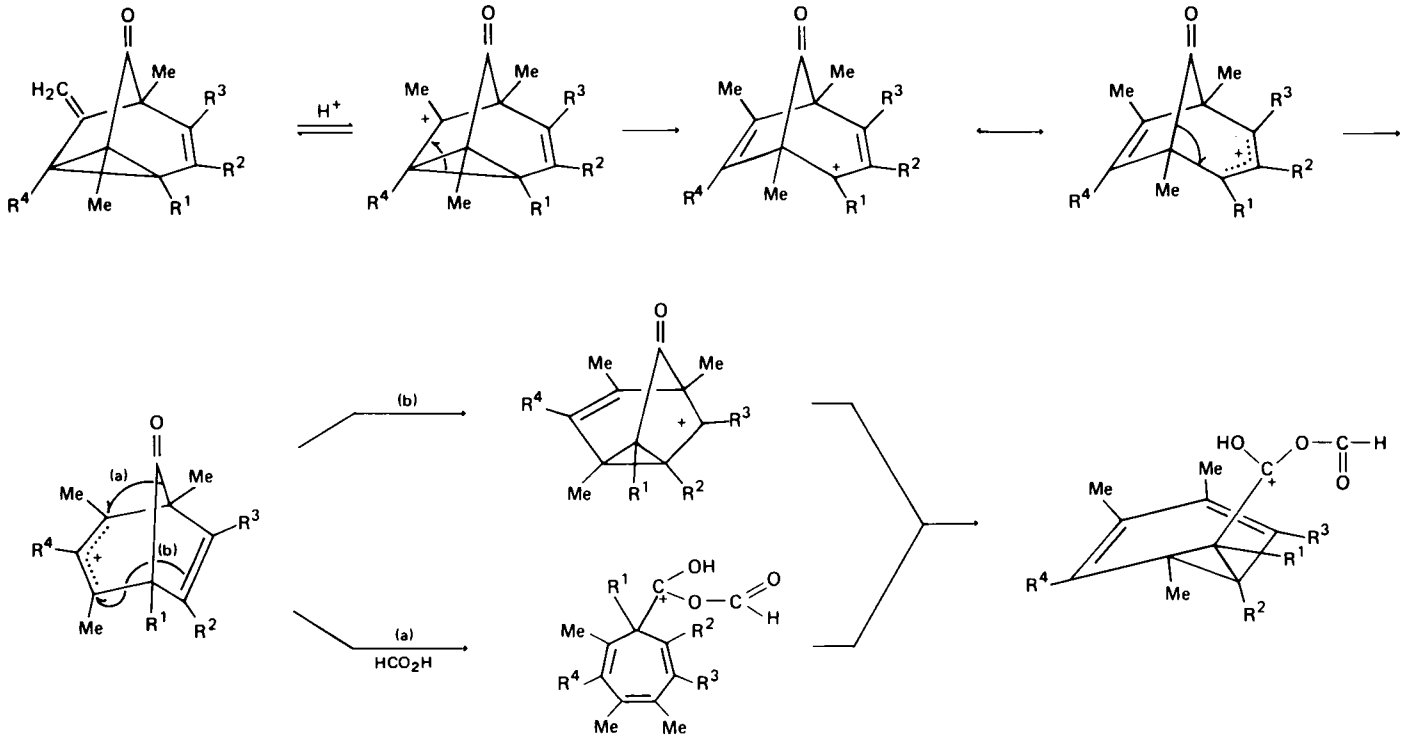


(367)

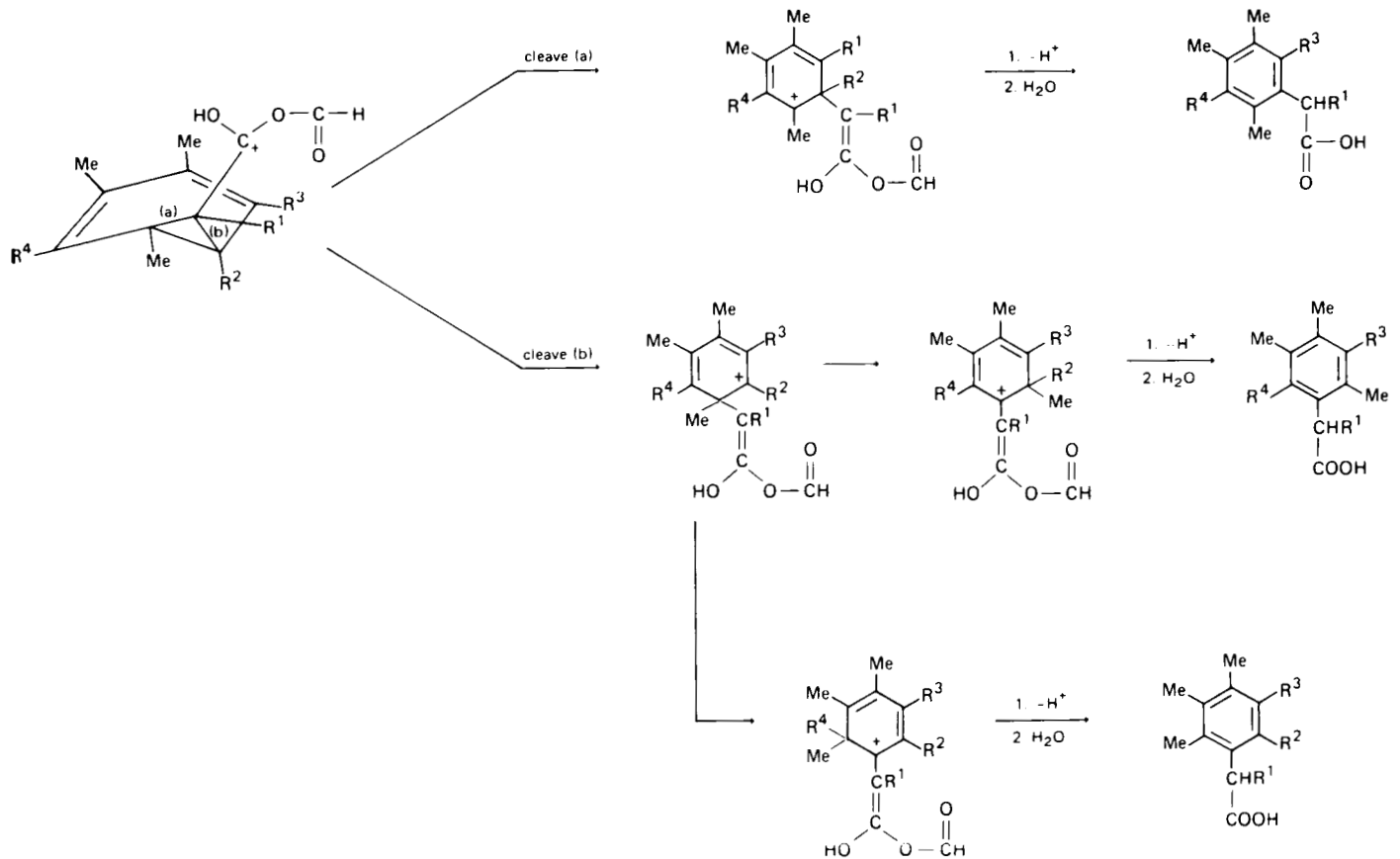
The base-catalysed hydrolysis reactions which lead to rearranged acids or esters have been applied to a variety of compounds. Coumarin dibromide has been converted to coumarilic acid in 82–88% yield upon treatment with potassium hydroxide followed by acidification (equation 368)[911]. Isatin has been converted



(368)

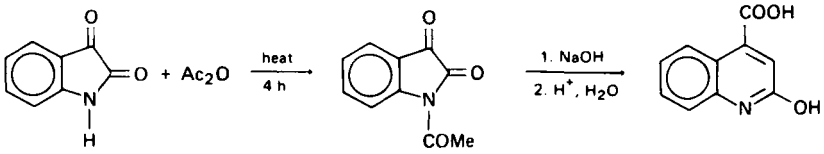


SCHEME 7(a).



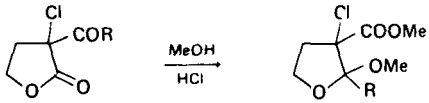
SCHEME 7(b).

to 2-hydroxycinchoninic acid in 70–73% yield via treatment of the intermediate *N*-acetylisatin with sodium hydroxide followed by acidification (equation 369)[912].



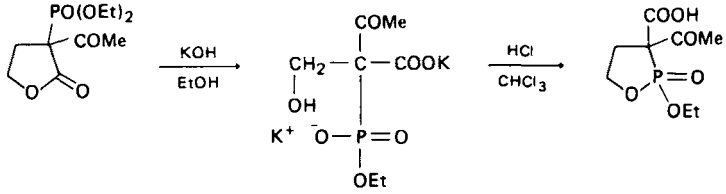
(369)

Base-catalysed hydrolysis of lactones has also led to rearranged acids as illustrated by the reports of Korte and coworkers. Based upon their initial findings that α-alkyl[913] and α-halogen-α-acyl lactones[914] upon treatment with hydrochloric acid in methanol afforded 2-methoxy-3-chloro-3-carbomethoxy tetrahydrofuran derivatives (equation 370), they then investigated the reaction of α-phosphonic acid



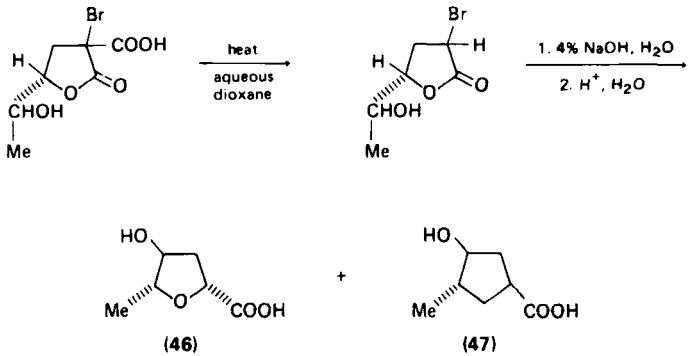
(370)

ester substituted α-acyl lactones. Korte found that treatment of the diethyl ester of α-acetyl-γ-butyrolactone-α-phosphonic acid with potassium hydroxide in ethanol followed by treatment with hydrochloric acid in chloroform afforded the ethyl ester of α-acetyl-α-carboxy-γ-phostone[915] via a ring-opened intermediate (equation 371).



(371)

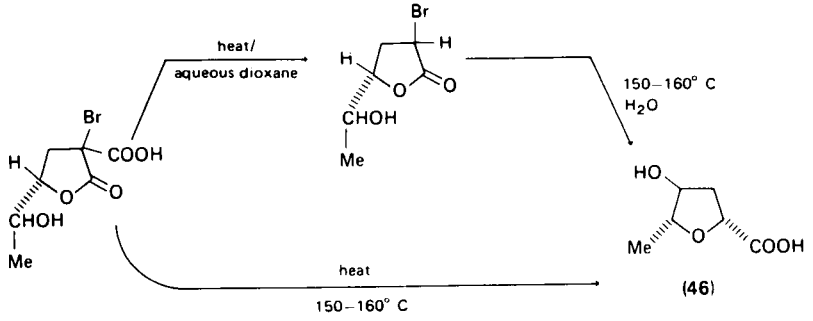
A similar rearrangement of α-bromo-α-carboxy-γ-substituted γ-butyrolactone to a stereochemical mixture of 4-hydroxy-5-methyl-2-tetrahydrofuroic acid has been reported[916] upon decarboxylation of the lactone in aqueous dioxane, followed by hydrolysis of the intermediate bromolactone with 4% sodium hydroxide (equation 372). A stereospecific synthesis of the *cis* isomeric acid **46**, can also be accom-



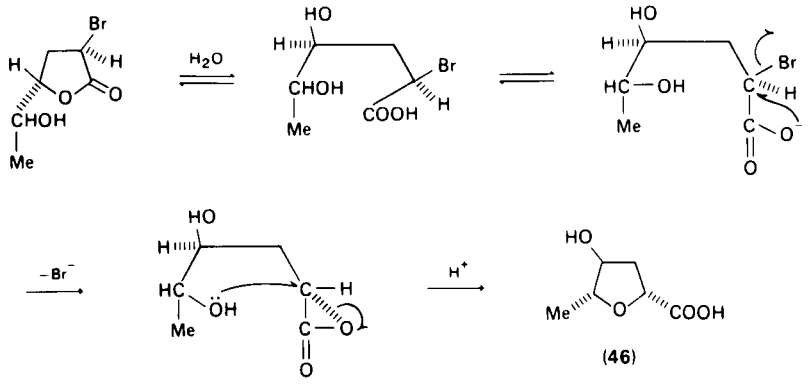
(372)

(46) (47)

plished by decarboxylation as above, followed by hydrolysis at 150–160°C in water, or, more directly, by decarboxylation of the starting lactone upon heating in a sealed tube at 150–160°C for one hour (equation 373). The mechanism for these rearrangements is shown in equation (374) assuming the *trans* configuration of the intermediate bromo lactone.



(373)



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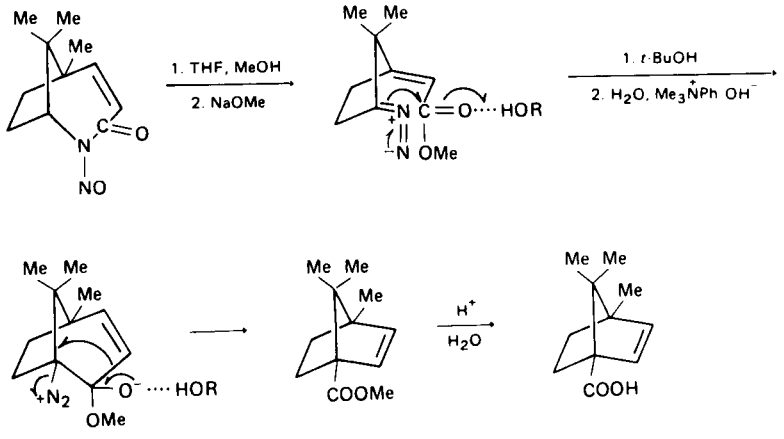
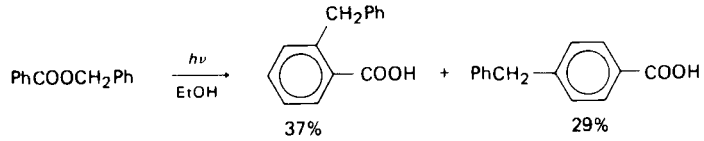


(375)

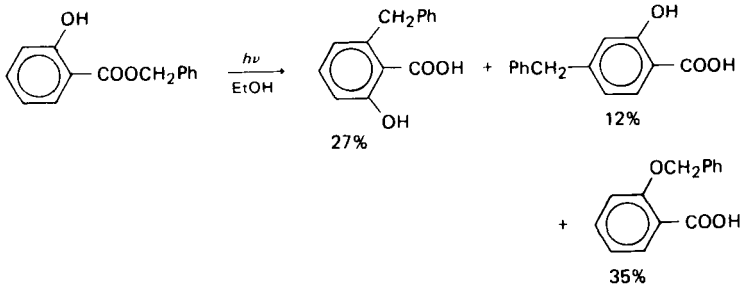
Base-catalysed rearrangements of bicyclic compounds have also been reported. Treatment[917] of 6,9,9-trimethyl-2-nitroso-2-azabicyclo[4.2.1]non-4-en-3-one with methanol in THF followed by reaction with sodium methoxide affords methyl *cis*-β-(3-diazo-1,2,2-trimethylcyclopentyl)acrylate, which upon reaction with *N,N,N*-trimethylanilinium hydroxide afforded a 90% yield of methyl 4,7,7-trimethylbicyclo[2.2.1]hept-2-ene-1-carboxylate. Acidification of the ester afforded 89% of the corresponding acid (equation 375). Additional studies in this series have also been reported[918].

d. Photochemical rearrangements. Photochemically-induced rearrangements for the production of acids and esters have been applied to a variety of compounds. In most types of photochemical rearrangements the presence of a substituent on the starting material, rather than simply effecting the rate of the reaction, actually causes a different product to be formed. For example, room-temperature photolysis of an ethanol solution of benzyl benzoate[919] affords only *ortho*- and *para*-benzylbenzoic acids (equation 376). However, when an *ortho*-hydroxy substituent



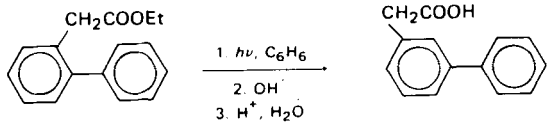
(376)

is present in the benzyl benzoate starting material, 2-benzyloxybenzoic acid is the major product formed upon photolysis (equation 377)[919].

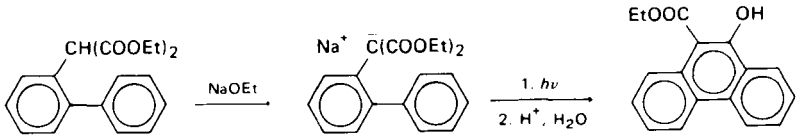


(377)

Similar results are obtained[920] upon photolysis of a benzene solution of *o*-biphenylyl acetate, which after hydrolysis and acidification affords *m*-biphenylylacetic acid (equation 378), while photolysis of the α-anion of diethyl *o*-biphenylylmalonate produces[920] ethyl 10-hydroxy-9-phenanthroate via intramolecular photoacylation of the intermediate enolate (equation 379). This type of photo-

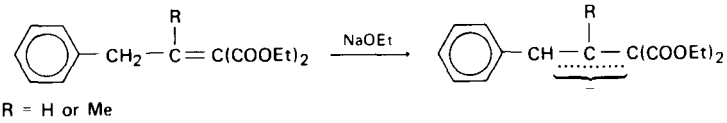


(378)



(379)

acylation was also observed[920] when the anion of phenylethylidenemalonic ester was photolytically ring-closed (equation 378). The mechanism used to explain these intramolecular photoacylation reactions (equations 381 and 382) requires that the non-bonding 2*p* electrons of the carbanion (or heteroatom Y) be delocalized onto the phenyl or biphenyl system in the electronically excited state producing an increase in the electron density at the *ortho* positions in the excited state of the enolate ion.



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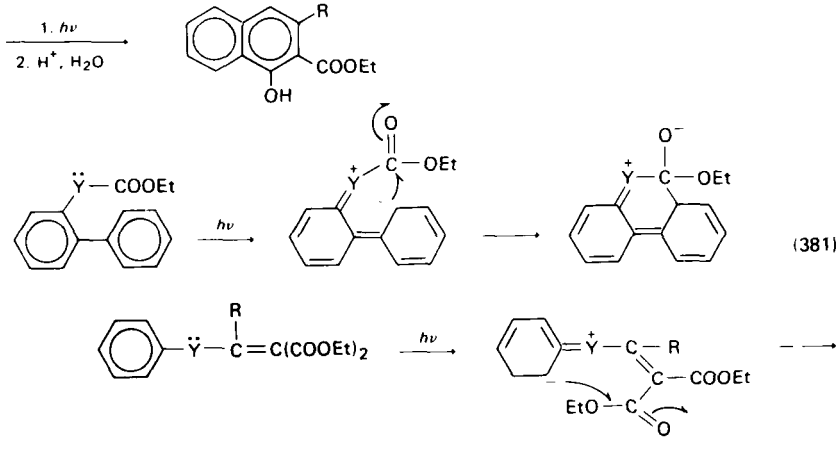
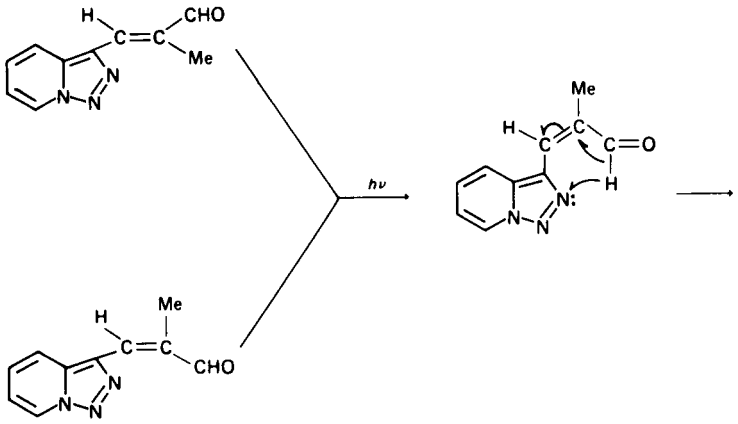


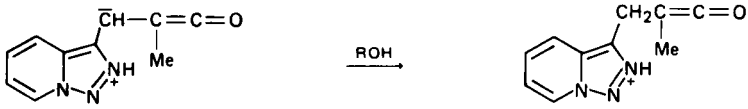
(381)

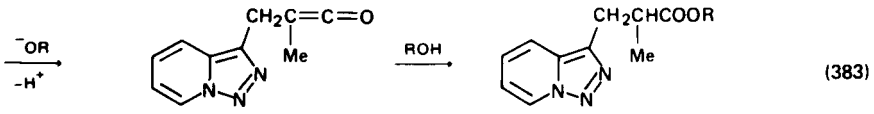
(382)

The presence of a lone electron pair has also been shown to be required in the photochemical conversion of *cis*- and *trans*-acraldehydes to methyl and *t*-butyl 3(3-*v*-triazolo[1,5-a]pyridyl-2-methylpropionate in 74 and 59% yields, respectively. The mechanism proposed for these conversions is shown in equation (383). A similar mechanism can be used to explain the conversion[921] of *v*-triazolylacraldehyde in 92% yield to methyl 3-(1-methyl-*v*-triazol-4-yl)propionate upon photolysis in methanol or in 29% yield to 3-(1-methyl-*v*-triazol-4-yl)propionic acid upon photolysis in water.

An interesting photochemically-induced ring-cleavage reaction[922] producing an acid has also been reported, in which 2,8-dioxo-1,3-diphenyl-1,2,3,8-tetrahydro-(cyclopenta-[a]-indene) has been converted in 39% yield to 1-oxo-2-(α-carboxybenzyl)-3-benzylidene indane (equation 384).

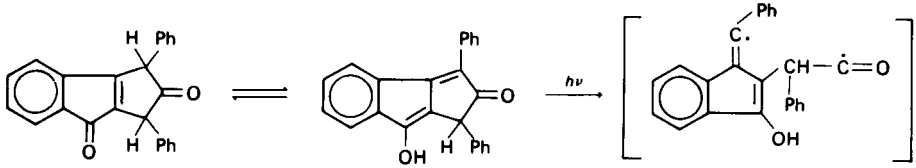


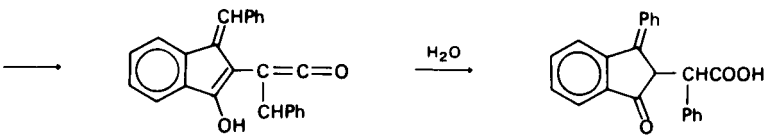




R = Me or *t*-Bu

(383)





(384)

III. SYNTHESIS OF ESTERS

A. Esters by Solvolytic Reactions

Direct conversion of carboxylic acids and acid derivatives into esters by reactions with hydroxylic compounds are designated here as solvolysis reactions. Included are reactions of acids with alcohols, alcoholyses of acyl halides, anhydrides, ketenes, nitrites and amides, and transesterifications. Reactions of carboxylate salts with alkylating agents, although not strictly solvolytic processes, are also included.

1. Direct esterification of acids

The most frequently encountered method for preparation of esters from carboxylic acids involves reaction of the free acid with an alcohol in the presence of a mineral acid catalyst at reflux (equation 385). Such reactions are equilibrium

$$R^1COOH + R^2OH \overset{H^+}{\rightleftharpoons} R^1COOR^2 + H_2O \qquad (385)$$

processes, and must be displaced toward the desired ester by use of an excess of one of the reactants, usually the alcohol, or by removal of water. Primary and secondary alcohols usually react satisfactorily, whereas tertiary alcohols and phenols participate poorly because of competing elimination and poor nucleophilicity, respectively. As would be expected for reactions which involve nucleophilic addition of the hydroxy component to the protonated carboxyl group of the acid, sterically hindered acids are esterified with difficulty under these conditions[923].

Among the catalysts used for direct esterification, sulphuric acid alone[924-926] or in the presence of molecular sieves[927,928], hydrogen chloride[929,930] and arylsulphonic acids[931-933] are the most popular. Acidic ion-exchange resins in conjunction with a dehydrating agent such as calcium sulphate are also effective catalysts[933,934]. Polymer-protected aluminium chloride, a complex between anhydrous aluminium chloride and polystyrene–divinylbenzene copolymer, can serve as both a Lewis-acid catalyst and a dehydrating agent to effect esterification of alkyl and aryl acids with primary and secondary alcohols under mild conditions[935]. Along similar lines, graphite bisulphate, an intercalated complex, prepared by electrolysis of 98% sulphuric acid with a graphite anode, functions very effectively as a catalyst for esterification of various acids with primary and secondary alcohols[936].

A great deal of attention has been focused on the use of boron trifluoride as a catalyst for esterification. Several different procedures can be used with this reagent. For example, methyl esters can be prepared from various acids by refluxing with two molecular equivalents of the commercial boron trifluoride–methanol complex in excess methanol[937]. Alternatively, boron trifluoride–etherate can be used as a catalyst for preparative-scale esterification. In these reactions the alkyl group of the resulting ester is not limited to methyl, as in the preceding case. Boron trifluoride etherate–alcohol esterifications are usually carried out by refluxing the acid with 1–2 equivalents of catalyst and a 10–15 molar excess of the appropriate alcohol. This mild, effective method has been designated in a recent review[938] as perhaps the most generally satisfactory procedure for direct esterification of carboxylic acids.

Trifluoroacetic anhydride can be used to promote rapid esterification of acids with both alcohols and phenols[939-943]. The mixed anhydride formed by reaction

of trifluoroacetic anhydride with the carboxylic acid is apparently the reactive intermediate. A related process involves treatment of a mixture of an acid and alcohol in pyridine with an aromatic sulphonyl chloride (equation 386)[944,945].

$$R^1COOH \xrightarrow[\text{pyridine}]{ArSO_2Cl} (R^1CO)_2O \xrightarrow{R^2OH} R^1COOR^2 \qquad (386)$$

This reaction proceeds through *in situ* formation of the symmetrical anhydride, which then reacts with the hydroxylic compound. Aliphatic and aromatic acids can be used, and phenols as well as tertiary alcohols afford high yields of esters.

Several acid-catalysed esterification procedures are especially useful for the preparation of phenyl esters. One of the most versatile involves treatment of a carboxylic acid with a phenol in the presence of 1–5 mole % of a mixture of boric and sulphuric acids in toluene, xylene, or sulpholane–xylene[946]. Azeotropic removal of water gives the phenyl esters in high yield. Neither sulphuric acid nor boric acid alone catalyses the reaction. Polyphosphate esters, prepared by reacting diethyl ether with phosphoric oxide in chloroform, can be used to promote aryl ester formation[947]. Diphenyl phosphite in pyridine also serves to effect formation of phenyl esters from free acids and phenols[948,949]. Triphenylphosphine ditriflate, obtained *in situ* from triphenylphosphine and trifluoromethanesulphonic acid, has been shown to be an efficient electrophilic catalyst for esterification of free acids with both phenols and tertiary alcohols[950].

If acidic conditions are to be avoided, a number of efficient procedures are available. For instance, dicyclohexylcarbodimide (DCCD)[951,952] or β-trichloromethyl-β-propiolactone[953] can be used to effect esterification of carboxylic acids with alcohols and phenols. Reaction of carboxylic acids with equimolar amounts of an alcohol and *N,N'*-carbonyldimidazole constitutes a mild procedure for the synthesis of various esters (equation 387)[954]. The acid reacts initially with *N,N'*-carbonyldiimidazole to evolve carbon dioxide and form an *N*-acylimidazole (imidazolide). This intermediate then acylates the alcohol. The acylation step is catalysed by basic reagents such as sodium ethoxide, alkali metal amide or imidazolyl sodium. Hindered acids and tertiary alcohols participate readily in these reactions.

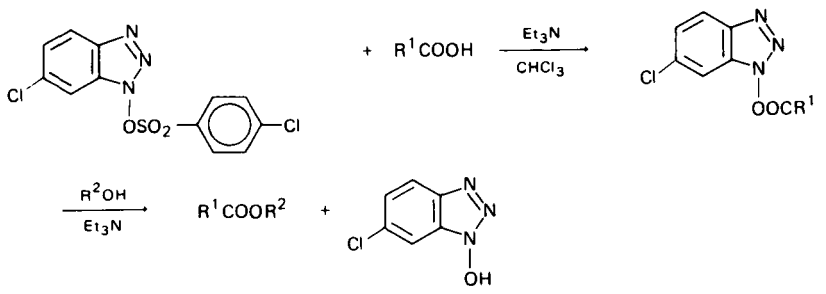
$$R^1COOH + \left(\begin{array}{c}N\\ \| \\ \text{C}\\ \diagdown\ \diagup\\ N\end{array}\right)_2 C{=}O \xrightarrow{-CO_2} R^1CO{-}N\begin{array}{c}\diagup\ \diagdown\\ \text{C}\\ \| \\ N\end{array} \qquad (387)$$

$$\xrightarrow[\text{base}]{R^2OH} R^1COOR^2$$

Esters can be prepared under neutral conditions at room temperature by the reaction of carboxylic acids with alcohols in presence of molar amounts of triphenylphosphine and diethyl azodicarboxylate (equation 388)[955]. Esterification of chiral alcohols by this procedure leads to inversion of configuration at the carbinol carbon[956].

$$R^1COOH + R^2OH \xrightarrow[Ph_3P,\ ether]{EtOOCN{=}NCOOEt} R^1COOR^2 + Ph_3PO + EtOOCNHNHCOOEt \qquad (388)$$

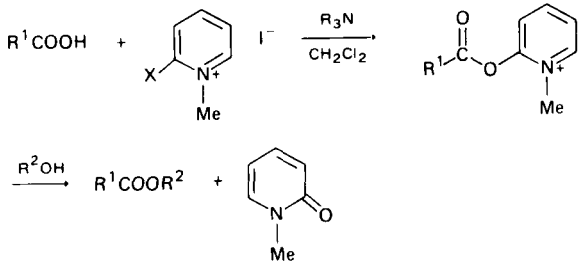
A mild esterification method for carboxylic acids employs sulphonate coupling reagents such as 6-chloro-1-*p*-chlorobenzensulphonyloxybenzotriazole (equation 389)[957]. This procedure consists of two steps, the first of which is condensation of



(389)

a carboxylic acid with the triazole to form an active carbamate-type ester. Alcoholysis of this intermediate with primary or secondary alcohols then affords the ester.

A new method for the preparation of esters, which is satisfactory for both hindered acids and tertiary alcohols, is based on the reaction of equimolar amounts of a carboxylic acid and an alcohol or phenol in the presence of 1.2 equivalents of 1-methyl-2-halopyridinium iodide and 2.4 equivalents of a tertiary amine (equation 390)[958]. The reaction proceeds by initial formation of a 2-acyloxypyridinium salt, which then reacts with the alcohol to produce the ester and *N*-methyl-2-pyridone.



(390)

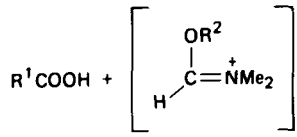
Reaction of carboxylic acids with diazoalkanes represents a widely used method for ester preparation (equation 391)[959–961]. However, the toxic and potentially explosive characteristics of these reagents renders them impractical for preparative-scale esterifications.

$$R^1COOH + R^2CHN_2 \longrightarrow R^1COCH_2R^2 + N_2 \qquad (391)$$

Several other esterification methods also utilize reagents other than alcohols as the source of the alkoxy function of the resulting esters. For instance, dialkyl acetals of *N*,*N*-dimethylformamide react with various acids to afford esters in good yields (equation 392)[962,963].

$$R^1COOH + H{-}C(OR^2)_2{-}NMe_2 \longrightarrow R^1COOR^2 + R^2OH + HCONMe_2 \qquad (392)$$

Dimethylformamide–dialkyl sulphate adducts react rapidly with various aliphatic and aromatic mono- and dicarboxylic acids to afford the corresponding esters (equation 393)[964].



$$R^1COOH + \left[\begin{array}{l} OR^2 \\ | \\ H\diagup C=\overset{+}{N}Me_2 \end{array}\right] R^2OSO_3^- \longrightarrow R^1COOR^2 + R^2OSO_3H + HCONMe_2 \quad (393)$$

Carboxylic acids are smoothly transformed into esters upon reaction with alkyl *t*-butyl ethers in the presence of proton-donating agents such as sulphuric acid or *p*-toluenesulphonic acid (equation 394)[632,966].

$$R^1COOH + R^2OBu\text{-}t \xrightarrow{H^+} R^1COOR^2 + CH_2{=}C(CH_3)_2 + H_2O \quad (394)$$

Trialkyl phosphites[965,966] can also serve as convenient esterifying agents, especially where strong acid catalysts are to be avoided.

Although several of the preceding methods can be used to prepare *t*-alkyl esters, the procedures employed most often consist of treatment of a carboxylic acid with an alkene in the presence of a strong mineral acid[967,968]. A recent synthesis of *t*-butyl esters involves reaction of the carboxylic acid with a mixture of isobutylene and *t*-butyl alcohol; the alcohol serves to prevent polymerization of the alkene during esterification[969].

2. *Alkylation of carboxylate salts*

Ester formation can be accomplished by treatment of carboxylate salts with a suitable alkylating agent as shown in equation (395). A number of satisfactory

$$R^1COO^-M^+ + R^2X \longrightarrow R^1COOR^2 + MX \quad (395)$$

procedures are available for accomplishing this type of esterification. The major differences between methods rest largely in the nature of the carboxylate salts and solvents employed. Alkyl halides and sulphonate esters are the most satisfactory alkylating agents. Dipolar, aprotic solvents such as DMF, DMAC, HMPA and DMSO accelerate the alkylations, but can be rather difficult to remove during isolation of the carboxylate ester. Most of the reactions listed in Table 42 proceed smoothly when the alkylating agent is primary, allylic or benzylic; however, elimination can become a serious side-reaction with secondary and tertiary alkylating agents. However, it has been found that mercury(II) acetate in diglyme reacts with *t*-butyl halides and α-phenylethyl chloride to afford the corresponding esters in the presence of triacyloxylboranes[999].

Phenacyl esters have been prepared in excellent yields by alkylation of carboxylate salts in the presence of catalytic amounts of crown ethers[1000]. The two-phase nature of these reactions makes product isolation quite convenient. Various diamines have also been found to activate carboxylate anions towards alkylation in two-phase media[1001].

Tetraalkylammonium carboxylates can be converted into esters by thermolysis in refluxing toluene[1002,1003]. Thus, phenyltrimethylammonium benzoate, prepared by titration of benzoic acid with trimethylanilinium hydroxide, affords methyl benzoate in 90% yield after brief refluxing in toluene (equation 396)[1002].

$$PhCOO^-\overset{+}{N}Me_3Ph \xrightarrow{\Delta} PhCOOMe + Me_2NPh \quad (396)$$

TABLE 42. Alkylations of carboxylate salts to form esters

Type of salt	Alkylating agent	Solvent	References
K^+, Na^+	RX	DMF	970–973
Na^+	MeI	DMAC	974
Na^+	EtI	Me_2CO	975
Na^+	RX	HOAc	976, 977
Na^+	$PhCH_2Cl$	EtOH	978
K^+, Na^+	Et_2SO_4	DMF, Me_2CO	979–981
Na^+	ROMs	DMF	982
K^+, Na^+	RX	HMPA	983–985
Na^+	$Et_3O^+BF_4^-$	H_2O	986
Ca^{2+}	MeI	DMSO	987
Ag^+	RX	Et_2O, HOAc	988–990
Cu^+	RX	C_6H_6, C_5H_5N	991–993
R_4N^+	RX	DMAC, DMF	994–996
R_4N^+	$Et_3O^+BF_4^-$	CH_2Cl_2	997
$Hg^{2\bullet}$	RX	ROH/H_2O	998

Ion-exchange resins containing quaternary ammonium groups can be used to effect ester synthesis by first passing the carboxylic acid through the column to form the carboxylate resin (equation 397). Esterification is then achieved by

$$\text{Resin}-\overset{+}{\text{N}}\text{Me}_3\bar{\text{O}}\text{H} + \text{R}^1\text{COOH} \longrightarrow \text{Resin}-\overset{+}{\text{N}}\text{Me}_3\text{R}^1\text{COO}^- \xrightarrow{\text{R}^2\text{X}} \text{R}^1\text{COOR}^2 + \text{Resin}-\overset{+}{\text{N}}\text{Me}_3\text{X}^- \quad (397)$$

stirring the resin with an alkylating agent in a suitable solvent. The product is isolated simply by filtering off the resin and removing the solvent[1004].

Esters can be prepared by reaction of sodium carboxylates with alkylchlorosulphites (equation 398)[1005]. This reaction has recently been shown to proceed by initial formation of a mixture of dialkyl sulphite and anhydride, which then react further to produce the ester[1006].

$$\text{R}^1\text{COO}^-\text{Na}^+ + \text{ClSO}_2\text{R}^2 \xrightarrow{\Delta} \text{R}^1\text{COOR}^2 + \text{SO}_2 \quad (398)$$

3. *Alcoholysis of acyl halides*

Reaction of acyl chlorides with alcohols or phenols (equation 399) provides a method for ester synthesis which does not suffer from the reversibility found in direct esterification. In cases where the starting acid is insensitive to the reaction conditions necessary for acid chloride formation, this is often the method of choice for ester preparation.

$$\text{R}^1\text{COCl} + \text{R}^2\text{OH} \longrightarrow \text{R}^1\text{COOR}^2 + \text{HCl} \quad (399)$$

It is frequently advantageous to conduct these alcoholysis reactions in the presence of a base, especially when tertiary alcohols are used. This prevents conversion of the labile alcohol to the chloride and reduces the possibility of acid-catalysed decomposition of the resulting *t*-alkyl ester. Aqueous sodium or

potassium hydroxide, pyridine[1007], 2,6-lutidine[1008], dimethylaniline[1009-1011], tertiary aliphatic amines[1012-1015], tetramethylurea[1016], as well as magnesium[1017,1018] can be used as acid scavengers.

Secondary alcohols react smoothly with acid chlorides in HMPA[1019] and liquid sulphur dioxide[1020] to form the expected esters without added base. A general procedure which avoids the necessity of adding a basic reagent, and also activates the alcohol component of the reaction, consists of first converting the alcohol to its sodium or lithium alkoxide with sodium hydride[1021] or *n*-butyllithium[1022] in an inert solvent, and then adding the acyl or aroyl chloride (equation 400). Such

$$R^1COCl + R^2_3CO^-M^+ \longrightarrow R^1COOCR^2_3 + MCl \qquad (400)$$

methods are especially useful for the preparation of esters from acid-sensitive alcohols. Thallium(I) salts of phenols are convenient intermediates for the synthesis of phenyl esters[1023]. Halomagnesium alkoxides react similarly with acid chlorides[1024].

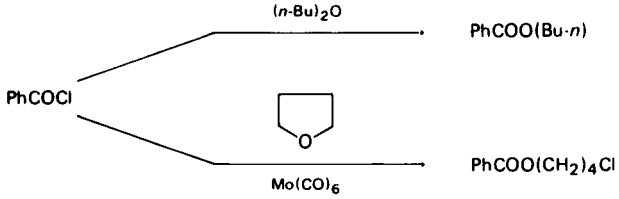
Addition complexes of acyl fluorides with antimony pentafluoride are highly reactive acylating agents which can be used to produce esters from alcohols and phenols (equation 401)[1025]. Acyl fluorides can be converted directly to esters by reduction with trialkylsilanes (equation 402)[1026]. Similar results are obtained with organotin hydrides[1027]. Reduction of acid chlorides with triphenyltin hydride in the presence of ketones can lead to direct production of secondary alkyl esters as shown in equation (403)[1028].

$$R^1CO^+\ SbF_6^- + R^2OH \xrightarrow{MeCN} R^1COOR^2 \qquad (401)$$

$$2\ RCOF + 2\ Et_3SiH \longrightarrow RCOOR + 2\ Et_3SiF \qquad (402)$$

$$EtCOCl + PhCOMe \xrightarrow[C_6H_6]{Ph_3SnH} EtCOOCH(Me)Ph \qquad (403)$$

Acid chlorides react with ethers in the presence of Lewis acids[1029] or transition-metal carbonyls[1030,1031] to form esters in satisfactory yields (equation 404).



(404)

4. *Alcoholysis of anhydrides*

Anhydrides function as useful acylating reagents for the synthesis of esters from alcohols and phenols (equation 405). Generally, anhydrides are less reactive than

$$(R^1CO)_2O + R^2OH \longrightarrow R^1COOR^2 + R^1COOH \qquad (405)$$

acyl halides in this capacity. With very reactive anhydrides such as trifluoroacetic anhydride, ester formation will occur rapidly in the absence of a catalyst. However, a variety of catalytic agents including sulphuric acid[1032], perchloric acid[1033], *p*-toluenesulphonic acid[1034], zinc chloride[1035,1036], sodium acetate[1037], sodium hydroxide[1038], tertiary aliphatic amines[1039] and pyridine[1040], have been employed. A combination of 4-dimethylaminopyridine and triethylamine is an especially effective catalyst[1041,1042]. As is the case with acid chlorides, alkoxides also react with anhydrides to produce esters[1043-1045]. Mixed anhydrides, prepared *in situ* from carboxylic acids and trifluoroacetic acid, react with various alcohols and phenols to afford numerous types of esters, including those as hindered as *t*-butyl mesitoate[1046]. Polymer-based anhydrides have recently been employed in the synthesis of benzoate esters[1047].

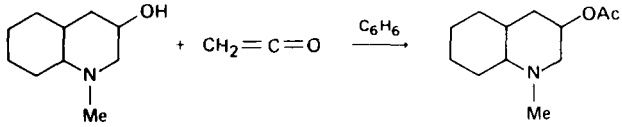
Acetic anhydride in the presence of ferric chloride reacts with a variety of ethers to form acetate esters (equation 406). Stereochemical results with optically active ethers suggest a dual mechanism involving *O*-acylation of the ether followed by dissociation of the more stable carbonium ion or displacement of an alkyl group by acetate[1048].

$$R^1-O-R^2 \xrightarrow[FeCl_3]{Ac_2O} R^1-\overset{+}{O}(C(=O)Me)-R^2 \xrightarrow[S_N2]{S_N1} MeCOOR^1 + MeCOOR^2 \quad (406)$$

5. *Alcoholysis of ketenes*

Ketenes react with alcohols and phenols to afford esters in an acylation process similar to those observed with acyl halides and anhydrides (equation 407). However, the procedure is used less frequently because ketenes are less readily available than the former reagents. The acylation of *N*-methyldecahydro-3-quinolinol is representative of such reactions (equation 408)[1049].

$$R^1C=C=O + R^2OH \longrightarrow R^1CHCOOR^2 \quad (407)$$

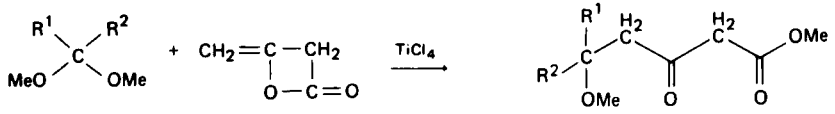


(408)

Diketene is a convenient reagent for the synthesis of β-keto esters possessing hindered alkoxy groups. Thus, *t*-butyl acetoacetate can be prepared from diketene and *t*-butyl alcohol (equation 409)[1050]. A recent paper describes a convenient procedure for carrying out these reactions in the presence of triethylamine[1051].

$$CH_2=C(-O-)(-CH_2-C=O) + Me_3COH \xrightarrow{NaOAc} CH_3COCH_2COOCMe_3 \quad (409)$$

Diketene has been found to react with acetals in the presence of titanium(IV) chloride to afford δ-alkoxy-β-keto esters in good yields (equation 410)[1052]. Titanium(IV) ethoxide effects condensation of ketene with ketones to produce β-hydroxy esters (equation 411)[1053].



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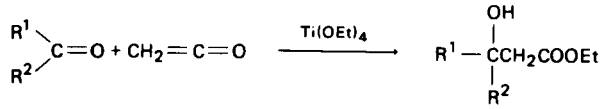
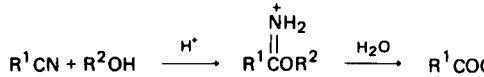


(411)

Ketene acetals[1054] and ketene thioacetals[1055] can be transformed into esters by acid-catalysed hydrolysis and alcoholysis, respectively.

6. *Alcoholysis of nitriles and amides*

Direct conversion of nitriles to esters can be accomplished without isolation of the intermediate acids. In most instances the cyano compound is first treated with an anhydrous alcohol in the presence of acid to form an imino ester, which is then hydrolysed to afford the desired ester (equation 412). The preparation of methyl 2,4,6-cycloheptatriene carboxylate[1056] may be viewed as representative of such reactions (equation 413). Additional details concerning the alcoholysis of nitriles may be found elsewhere[1057].



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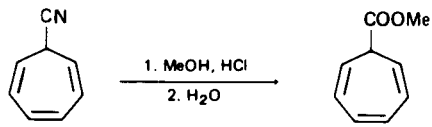
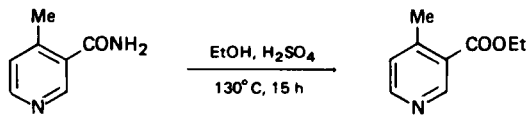


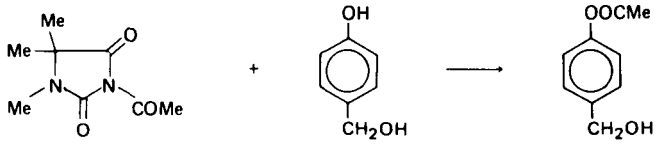
(413)

Alcoholysis of amides is encountered rather infrequently since it is much less facile than alcoholysis of more reactive acid derivatives. For example, conversion of benzamide to methyl benzoate requires prolonged treatment of the amide with methylpolyphosphate[1058] or methanol and boron trifluoride[1059] at relatively high temperatures. Preparation of ethyl 4-methylpyridine carboxylate from 4-methylnicotinamide by means of absolute ethanol and concentrated sulphuric acid also requires rather stringent conditions (equation 414)[1060].



(414)

Milder conditions can be used for alcoholysis if certain activated amides are employed. For instance, 3-acetyl-1,5,5-trimethylhydantoin reacts smoothly with *p*-hydroxybenzyl alcohol to afford the phenyl ester (equation 415)[1061]. It is interesting to note that the phenolic hydroxyl group reacts in preference to the alcohol function.



(415)

A convenient method for the synthesis of esters from secondary amides involves initial conversion of the amides into *N*-nitroso derivatives, which then undergo thermal elimination of nitrogen (equation 416)[1062,1063].

$$R^1CONHR^2 \xrightarrow[Ac_2O]{NaNO_2} R^1\underset{\displaystyle NO}{\overset{|}{C}}ONHR^2 \xrightarrow{\Delta} R^1COOR^2 + N_2 \qquad (416)$$

Amides have also been reported to yield esters on treatment with alkyl halides and water[1064].

7. *Transesterification*

Two general types of transesterification procedures are employed in ester synthesis. In the first of these, an ester is allowed to react with an alcohol in the presence of an appropriate acidic or basic catalyst (equation 417). The equilibrium

$$R^1COOR^2 + R^3OH \underset{\text{or } B^-}{\overset{H^+}{\rightleftharpoons}} R^1COOR^3 + R^2OH \qquad (417)$$

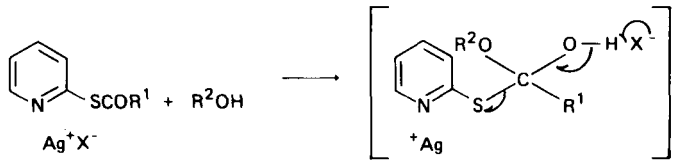
is shifted toward the desired ester by the use of excess alcohol and/or removal of one of the products by fractional distillation. Isopropenyl acetate is especially attractive as a source of acetate esters since acetone, formed as a by-product of the exchange, can be easily distilled from the reaction mixture[1065].

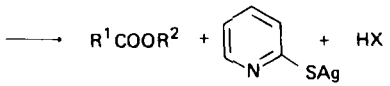
Common catalysts for transesterification include sulphuric[1066] and *p*-toluenesulphonic[1067] acids, as well as metal alkoxides[1067,1068]. More recently[1068], boron tribromide has been used to catalyse transesterification under mild conditions using both aliphatic alcohols and phenols. Among the newer examples of basic catalysts, tributyltin alkoxides[1069] and anion-exchange resins[1070] have been found to be effective. The latter reagents permit transesterification of esters of amino acids or peptides at room temperature. Transesterifications can also be accomplished in good yields by carrying out the reactions with potassium alkoxides in a Soxhlet apparatus containing molecular sieves to remove the displaced alcohol[1071].

Potassium cyanide-catalysed transesterification appears to be the preferred method for unsaturated esters which are prone to undergo double-bond migration or *cis/trans* isomerization with strong acids and bases[1072].

A mild new method for ester synthesis based on transesterification consists of silver ion-induced reaction of alcohols with 2-pyridyl esters of thiocarboxylic acids (equation 418)[1073].

Transesterification can be carried out by allowing an ester to react with an excess of a free carboxylic acid (equation 419). This procedure may be viewed as an exchange of carboalkoxy groups between an ester and an acid. Thus, the alkoxy groups of the reactant and product esters are identical. This type of transesterification method is especially useful for the preparation of vinyl esters. Such reactions



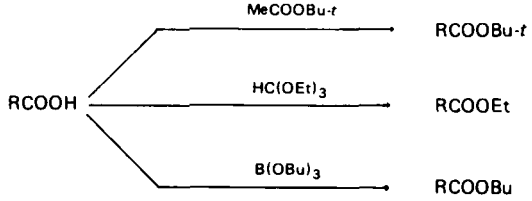


(418)

$$R^1COOR^2 + R^3COOH \longrightarrow R^3COOR^2 + R^1COOH \qquad (419)$$

are usually catalysed by mercury(II) salts[1074,1075]. The synthesis of vinyl laurate[1074] from lauric acid and vinyl acetate may be taken as representative (equation 420). Isopropenyl acetate participates in similar reactions with carboxylic acids[1076]. *t*-Butyl acetate[1077], triethyl orthoformate[1078] and alkyl borates[1079] have been used in transesterifications as shown in equation (421).

$$CH_3(CH_2)_{10}COOH + CH_3COOCH{=}CH_2 \xrightarrow[H_2SO_4]{Hg(OAc)_2} CH_3(CH_2)_{10}COOCH{=}CH_2 + CH_3COOH \qquad (420)$$



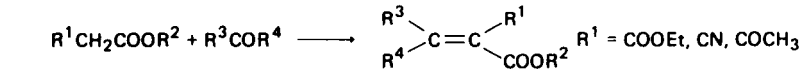
(421)

B. Esters by Condensation Reactions

Reactions involving carbanion intermediates play an important role in the synthesis of carboxylic acid esters. Many of the condensations discussed previously as routes to carboxylic acids can be adapted to the preparation of esters.

1. Knoevenagel reaction

This reaction involves treatment of an aldehyde or ketone with an active methylene compound in the presence of a catalytic amount of ammonia or an amine (primary or secondary) along with a small amount of a carboxylic acid (equation 422). If the active hydrogen component is diethyl malonate, ethyl

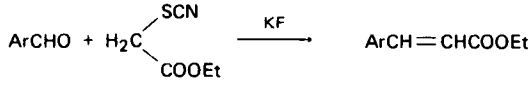


(422)

cyanoacetate or ethyl acetoacetate the product is an α,β-unsaturated ester. Malonic esters condense smoothly with aldehydes and reactive ketones such as acetone and

cyclohexanone; however, less reactive ketones require the more acidic substrate, ethyl cyanoacetate for successful formation of α,β-unsaturated esters. Numerous examples of ester syntheses may be found in the extensive review articles dealing with the Knoevenagel reaction[1080-1082].

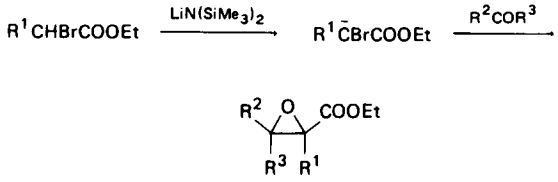
One of the most significant recent developments dealing with the Knoevenagel reaction is the finding that titanium chloride can serve as an effective catalyst for condensations involving both aldehydes and ketones[1083-1085]. Potassium fluoride has also been used in Knoevenagel-type condensations of aryl aldehydes with ethyl isothiocyanatoacetate[1086] to afford cinnamate esters (equation 423).



(423)

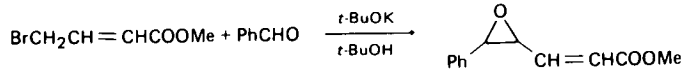
2. *Darzens reaction*

As a method for ester synthesis, the Darzens condensation finds its most frequent applications in the preparation of glycidic esters. Several recent observations concerning the Darzens reaction include the finding that lithium bis(trimethylsilyl)amide is an effective base for generating α-carbanions from α-bromo esters (equation 424)[1087]. A vinylogous counterpart of the normal Darzens con-



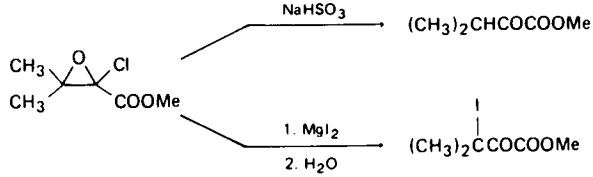
(424)

densation occurs when methyl 4-bromocrotonate is reacted with benzaldehyde in the presence of potassium *t*-butoxide (equation 425)[1088].



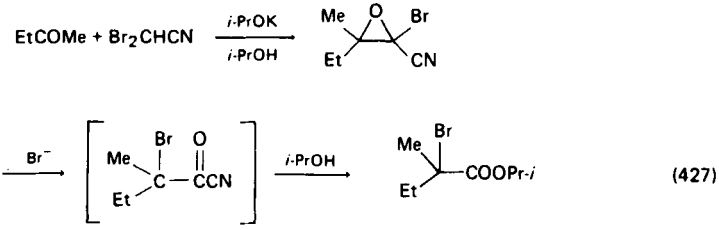
(425)

α-Chloroglycidic esters, prepared by Darzens condensations of aldehydes and ketones with α,α-dichloroacetates, can be converted to α-keto esters and β-iodo-α-keto esters by means of sodium bisulphite and magnesium iodide, respectively (equation 426)[1089].

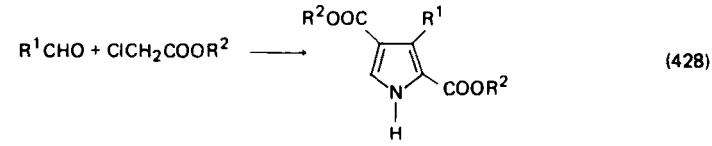


(426)

The synthesis of α-bromo esters can be accomplished through a Darzens-type condensation using dibromoacetonitrile as the active hydrogen component (equation 427)[1090].



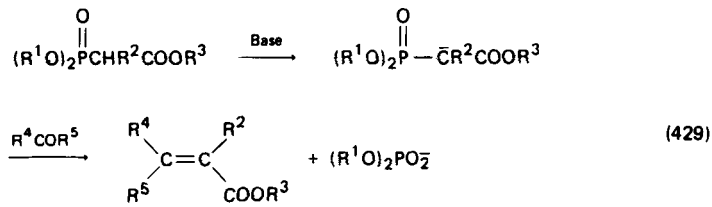
A new method for the preparation of 2,4-dicarboalkoxypyrroles involves Darzens condensation of α-chloro esters with aldehydes in the presence of 1,8-diazobicyclo-[5.4.0]undec-7-ene (equation 428)[1091].



(428)

3. *Wittig-type reactions*

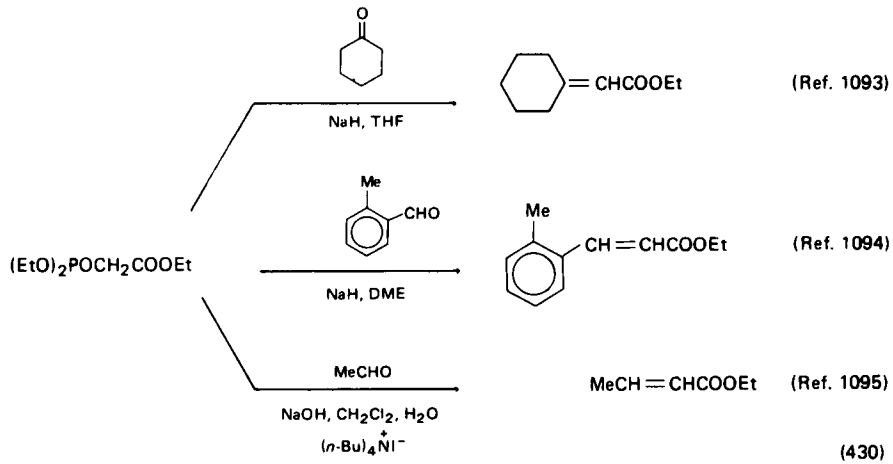
Among the various combinations of reactants which have been employed in Wittig-type syntheses of esters[125,126], the Wittig–Horner[1092] reaction is encountered most frequently because of its convenience and versatility. This reaction utilizes resonance-stablized carbanions derived from carboalkoxymethylphosphonate esters, which can then be reacted with aldehydes and ketones to produce α,β-unsaturated esters (equation 429). The reactions shown in equation (430) represent recent examples of the Wittig–Horner reaction using the carbanion derived from carboethoxymethyl diethylphosphonate. Numerous other well-tested examples of reactions employing this and related phosphonate carbanions in the synthesis of α,β-unsaturated esters are available[1096–1099].

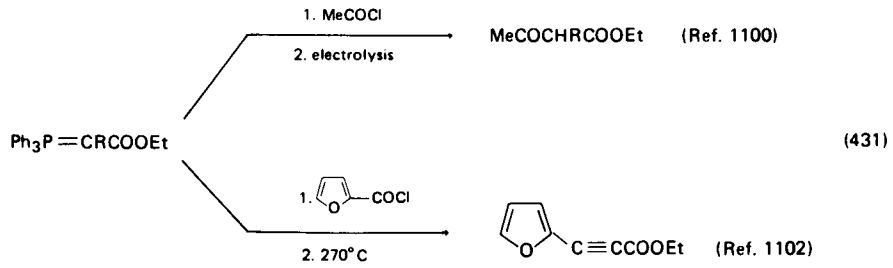


(429)

Carboalkyoxymethylenephosphoranes can be employed in the preparation of β-keto esters and α,β-acetylenic esters by first subjecting them to *C*-acylation with acid chlorides followed by electrolytic reduction[1100] and thermolysis[1101,1102], respectively (equation 431). Reactions with epoxides lead to α,β-unsaturated esters[1103].

α, -Unsaturated esters can also be prepared by reacting α-bromo or α-iodo esters wit'⁄two equivalents of a methylenephosphorane (equation 432)[1104]. In this case the alkylating agent, rather than the phosphonium ylide, provides the ester function.





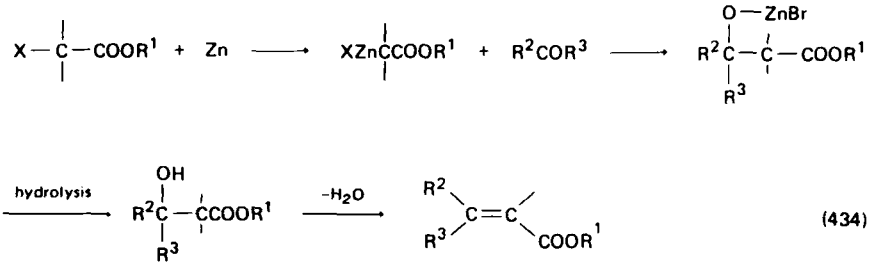
$$2\ Ph_3P{=}CHPr + MeCHICOOEt \longrightarrow PrCH{=}CMeCOOEt \qquad (432)$$

An attractive alternative to the Wittig–Horner reaction employs lithio salts of α-trimethylsilyl esters (equation 433)[1105-1107].

4. Reformatsky reaction

In the Reformatsky reaction an aldehyde or ketone is allowed to react with an α-halo ester in the presence of metallic zinc to afford a β-hydroxy ester. Dehydration of the hydroxy esters can be accomplished to afford α,β-unsaturated esters. This reaction (equation 434) has been reviewed extensively[1108-1110].

Improved yields in the Reformatsky reaction have been obtained recently by using a continuous-flow apparatus[1111] or activated zinc obtained by reduction of zinc chloride with potassium metal in THF[1112].

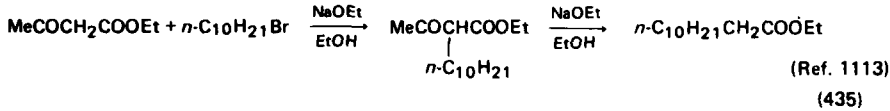


(434)

In connection with the use of the Reformatsky reaction as a synthetic route to β-hydroxy esters, it should be noted that reactions of carbonyl compounds with α-anions derived from esters provides a very attractive alternative, in that the α-anion method (Section III.B.7) can often be completed more quickly and in higher yields than the Reformatsky reaction.

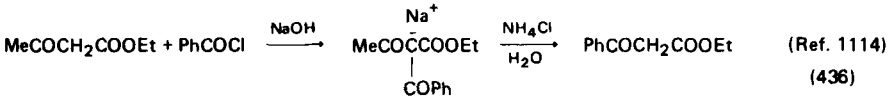
5. *Acetoacetic ester synthesis*

Ethyl acetoacetate is an important starting material for the synthesis of substituted acetate esters because of the ease with which alkylations can be effected at the active methylene position. Selective cleavage of the acetyl function completes the synthesis. It is important to prevent ester hydrolysis during acetyl cleavage, or the resulting β-keto acid may decarboxylate to generate ketonic products at the expense of ester formation. Ammonium hydroxide and alkali metal alkoxides are especially effective for this purpose. Reactions (435)–(437) are typical of acetoacetic ester syntheses of simple α-substituted acetates and β-keto esters.



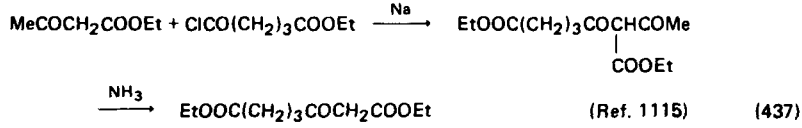
(Ref. 1113)

(435)



(Ref. 1114)

(436)

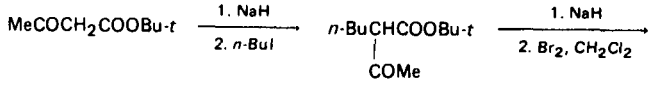


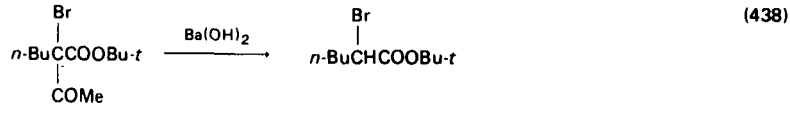
(Ref. 1115) (437)

α-Bromo esters can be prepared from *t*-butyl acetoacetate as shown in equation (438); acid-catalysed decomposition of the *t*-butyl ester gives the α-bromo acid[1116].

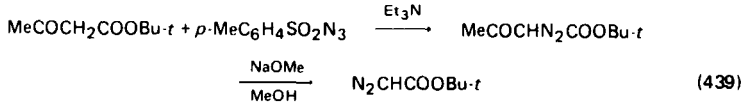
Reaction of *t*-butyl acetoacetate with *p*-toluenesulphonyl azide in the presence of triethylamine, followed by sodium methoxide-catalysed cleavage of the acetyl group affords *t*-butyl diazoacetate (equation 439)[1117].

The discovery[1118] that ethyl acetoacetate can be converted into its 1,3-dicarbanion by means of potassium amide in liquid ammonia has resulted in a number of



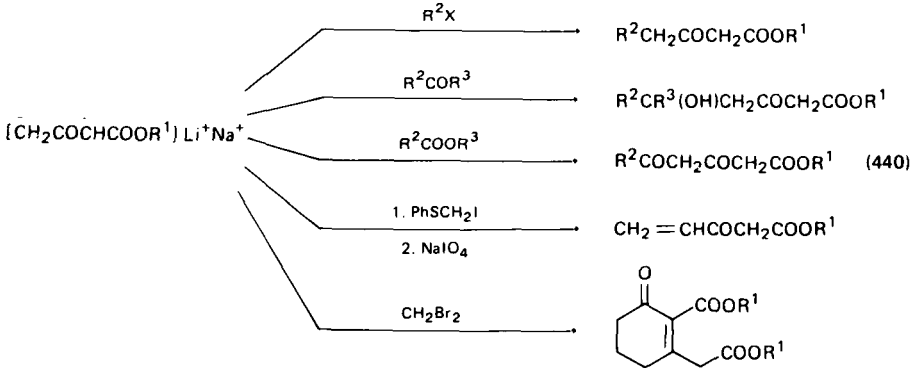


(438)



(439)

interesting new syntheses of β-keto esters based on condensation of this intermediate with electrophilic reagents (equation 440). The most satisfactory method



(440)

for dianion formation involves first treating ethyl acetoacetate with sodium hydride to generate the monoanion, and then adding an equivalent of *n*-butyllithium to remove a terminal methyl hydrogen[1119]. Reaction of the resulting sodiolithio salt with alkyl halides affords homologated β-keto esters resulting from alkylation at the original methyl group of the starting β-keto ester[1119]. Condensations with aldehydes and ketones produce δ-hydroxy-β-keto esters, which can be dehydrated to γ,δ-unsaturated β-keto esters[1120,1121]. Acylations with aromatic and aliphatic esters provide a route to β,δ-diketo esters[1122]. Treatment of the dianion of methyl acetoacetate with iodomethyl phenyl sulphide, followed by periodate oxidation of the resulting sulphide affords methyl 3-oxo-4-pentenoate[1123]. Alkylation of the same dianion with methylene bromide results in coupling, then intramolecular aldol condensations to give 2-carbomethoxy-3-carbomethoxymethyl-2-cyclohexanone[1124].

In connection with the utilization of β-keto esters as synthetic intermediates, it should be noted that methyl acetoacetate can be α-alkylated with allylic and benzylic halides under conditions of phase-transfer catalysis[1125], and with certain allyl ethers in the presence of sodium phenoxide and palladium(II) chloride complexes with triphenylphosphine[1126].

6. Malonic ester synthesis

As discussed earlier, the malonic ester synthesis is easily adapted to the preparation of various types of acids. However, the synthesis of simple esters is not so straightforward, since hydrolysis of substituted malonic esters generally results in cleavage of both ester groups to form malonic acids, which readily decarboxylate to give the appropriately substituted acetic acids. Therefore, in order to obtain esters as the ultimate products of a normal malonic ester synthesis, a final esterification step is required. This problem can be circumvented by several procedures which permit selective removal of one of the ester groups without affecting the other. The general approach is as shown in equation (441). Among the reagents which can be

$$CH_2(COOEt)_2 \xrightarrow[2.\ RX]{1.\ base} RCH(COOEt)_2 \longrightarrow RCH_2COOEt \qquad (441)$$

employed for monodecarboethoxylation of malonic esters are sodium chloride in aqueous DMSO[1127], and sodium cyanide in DMSO[1128]. Acylation of the lithium salt of ethyl trimethylsilylmalonate with α,β-unsaturated acid chlorides, followed by hydrolytic cleavage of the trimethylsilyl ester, gives unsaturated β-keto esters (equation 442)[1129]. An interesting new procedure for preparing simple esters

$$LiCH(COOSiMe_3)(COOEt) + CH_3CH{=}CHCOCl \xrightarrow[2.\ H_2O]{1.\ Et_2O,\ DME} CH_3CH{=}CHCOCH_2COOEt \qquad (442)$$

involves treatment of ethyl hydrogen malonate with two equivalents of lithium isopropylcyclohexylamide (LICA) to produce the dilithio salt (equation 443). Alkylation of the salt is then followed by decarboxylation to form α-substituted esters[1130].

$$H_2C(COOH)(COOEt) \xrightarrow{LICA} LiCH(COOLi)(COOEt) \xrightarrow[2.\ -CO_2]{1.\ RX} RCH_2COOEt \qquad (443)$$

α-Substituted acrylates can be prepared by Mannich condensations of monosubstituted malonic esters with dimethylamine, methylation of the resulting dimethylaminomethyl derivatives, and finally, decomposition of the resulting quaternary ammonium salts (equation 444)[1131].

$$RCH(COOMe)_2 \xrightarrow[2.\ MeI]{1.\ Me_2NH,\ HCHO} RC(COOMe)_2(CH_2\overset{+}{N}Me_3\ I^-) \xrightarrow[75^\circ C]{DMF} CH_2{=}CRCOOMe \qquad (444)$$

7. From α-anions of esters

Stoichiometric conversion of aliphatic esters to α-anions by simple acid–base reactions is often hampered by self-condensations or attack of the basic reagent at the carboalkoxy function. These problems can be overcome to some extent by using *t*-butyl esters with lithium amide in liquid ammonia as the base. Under these conditions, *t*-butyl acetate can be converted to its α-lithio salt in concentrations satisfactory for aldol condensations with various aldehydes and ketones to give β-hydroxy *t*-butyl esters (equation 445)[1132]. Other acetate esters also yield lithio salts, which react similarly with carbonyl compounds[1133–1137].

$$CH_3COOBu\text{-}t \xrightarrow[NH_3]{LiNH_2} LiCH_2COOBu\text{-}t \xrightarrow[2.\ H_2O]{1.\ R^1COR^2} R^1R^2C(OH)CH_2COOBu\text{-}t \quad (445)$$

The discovery that ethyl acetate, as well as numerous other aliphatic esters, can be converted quantitatively to α-lithio enolates by means of lithium bis(trimethylsilyl) amide[1138], lithium isopropylcyclohexylamide (LICA)[1139], or certain other lithium dialkyl amides in THF has resulted in the development of a number of new ester syntheses. The major advantages of these procedures are that they are easy to carry out and utilize readily available starting materials.

Alkylations[1140,1141] of ester enolates proceed readily to provide mono-, di- and trisubstituted acetates (equation 446), thereby presenting an attractive alternative to the malonic and acetoacetic ester syntheses. Lithio salts of α,β-unsaturated esters undergo alkylation at the α-position to give β,γ-unsaturated esters (equation 447)[1141,1142].

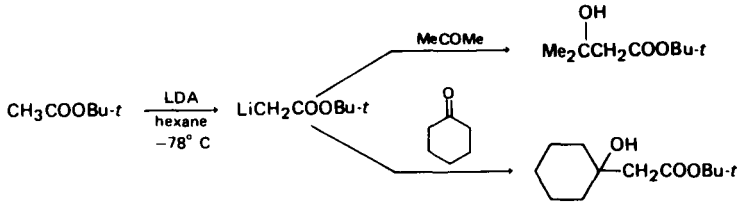
$$LiCH_2COOR^4 + R^1X \longrightarrow R^1CH_2COOR^4 \quad (446a)$$

$$R^1CHLiCOOR^4 + R^2X \longrightarrow R^1R^2CHCOOR^4 \quad (446b)$$

$$R^1R^2CLiCOOR^4 + R^3X \longrightarrow R^1R^2R^3CCOOR^4 \quad (446c)$$

$$CH_3CH{=}CHCOOEt \xrightarrow[2.\ MeI]{1.\ LDA} CH_2{=}CHCHMeCOOEt \quad (447)$$

Condensations of α-lithio esters, prepared in THF–hexane, with aldehydes and ketones afford β-hydroxy esters[1143–1145], in yields which surpass those obtained in Reformatsky reactions. An interesting example of such a reaction is found in the conversion of *t*-butyl acetate to its stable, crystalline lithium salt, which then reacts with acetone or cyclohexanone in toluene at 0°C to give the desired β-hydroxy ester in quantitative yield (equation 448)[1146].



(448)

β-Keto esters are available from ester enolates by reactions with acid chlorides (equation 449)[1147]. When the *O*-silyl ketene acetal prepared from lithio ethyl acetate and *t*-butyldimethylchlorosilane is allowed to react with acyl halides, β-keto esters are obtained upon hydrolysis with dilute hydrochloric acid (equation 450)[1148].

$$Me_2CHCOOEt \xrightarrow[2.\ PrCOCl]{1.\ LICA,\ -78°\ C} PrCOCMe_2COOEt \quad (449)$$

$$CH_2{=}C(OSiMe_2Bu\text{-}t)(OEt) \xrightarrow[2.\ H_3O^+]{1.\ RCOCl/Et_3N} RCOCH_2COOEt \quad (450)$$

α-Halo esters can be prepared by addition of ester enolates to THF solutions of iodine or bromine at −78°C (equation 451)[1149].

$$LiCHBuCOOEt + I_2 \xrightarrow[-78^\circ C]{THF} BuCHICOOEt \qquad (451)$$

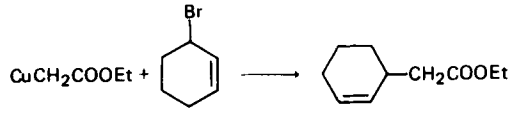
The synthesis of α-hydroxy esters from ester enolates can be accomplished by oxidation with molybdenum peroxide complexed with pyridine and hexamethylphosphoramide (HMPA) (equation 452)[1150]

$$R^1CHLiCOOR^2 \xrightarrow{MoO_5 \cdot Py \cdot HMPA} R^1CH(OH)COOR^2 \qquad (452)$$

Reaction of lithio esters with copper(II) salts results in oxidative dimerization to afford succinate esters in yields of 20–95% (equation 453)[1151]. In a related

$$2\ \mathrm{Li\overset{|}{\underset{|}{C}}COOR} + 2\ CuBr_2 \xrightarrow[-78^\circ C]{THF} ROOC\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}COOR \qquad (453)$$

process, it has been found that copper(I) ester enolates, prepared from the lithio salts and copper(I) iodide in THF, undergo dimerization on exposure to oxygen[1152]. These copper enolates also participate in coupling reactions with allylic halides to furnish γ,δ-unsaturated esters (equation 454).



(454)

α,β-Unsaturated esters can be synthesized from saturated esters by first preparing the lithium enolate, allowing it to react with dimethyl disulphide, oxidizing the resulting α-methylthio ester to the α-methylsulphinyl derivative, and then subjecting the sulphoxide to thermal elimination (equation 455)[1153].

$$\mathrm{PrCHCH_2COOMe} \xrightarrow[2.\ Me_2S_2]{1.\ LICA,\ THF,\ -78^\circ C} \mathrm{PrCHCHCOOMe} \xrightarrow[MeOH,\ H_2O]{NaIO_4}$$
(Et; SMe)

$$\mathrm{PrCHCHCOOMe} \xrightarrow[-MeSOH]{120^\circ C} \mathrm{Pr(H)C{=}C(Et)COOMe} \qquad \text{(Ref. 1153)} \qquad (455)$$
(SOMe; Et)

In a related procedure, the carbanion derived from methyl α-phenylsulphinylacetate is alkylated, and the resulting α-alkyl derivatives are then subjected to elimination (equation 456)[1154]. The magnesium halide derivatives of ethyl

$$PhSO\overline{C}HCOOMe + RCH_2X \xrightarrow{HMPA} PhSO\overset{CH_2R}{\underset{|}{C}}HCOOMe \xrightarrow{75-85^\circ C} RCH{=}CHCOOMe \qquad (456)$$

α-phenylsulphinylacetate react with aldehydes to give β-keto esters (equation 457)[1155].

$$\mathrm{PhSO\underset{\underset{MgX}{|}}{CHCOOEt} + RCHO \longrightarrow RC\underset{\underset{OH}{|}}{H}\overset{\overset{SOPh}{|}}{C}HCOOEt \longrightarrow RCOCH_2COOEt} \qquad (457)$$

Another procedure for synthesizing α,β-unsaturated esters involves reaction of ester enolates with phenylseleninyl chloride, followed by peroxy acid oxidation of the α-phenylseleno ester to the selenoxide, which spontaneously decomposes at room temperature to give the unsaturated ester (equation 458)[1156].

$$\mathrm{RCH_2CH_2COOEt \xrightarrow[2.\ PhSeCl]{1.\ LICA} RCH_2\overset{\overset{SePh}{|}}{C}HCOOEt \xrightarrow[EtOAc]{MeCOOOH}}$$

$$\mathrm{RCH(O)\text{—}CH(SePh)COOEt \xrightarrow{-PhSeOH} RCH{=}CHCOOEt} \quad \text{(Ref. 1156)} \qquad (458)$$

A recent publication summarizes reactions of ester enolates with various electrophiles, including most of those mentioned above[1157].

8. *Michael reactions and related conjugate additions*

As a method for ester synthesis, the Michael reaction follows the same general patterns as outlined for the preparation of acids. Thus, if the acceptor is an α,β-unsaturated ester, conjugate addition of a nucleophilic addend (A) produces an ester elaborated at the β-position (equation 459). Alternatively, if the addend is the α-anion of a mono- or diester, and the acceptor contains an appropriate anion-stabilizing group (B), carbon–carbon bond formation occurs at the α-position of the ester (equation 460). Numerous examples of such reactions may be found in the previously cited reviews of the Michael reaction[192].

$$\mathrm{>C{=}C(COOR)\text{—} + A \longrightarrow \text{—}\overset{\overset{A}{|}}{C}\text{—}CHCOOR} \qquad (459)$$

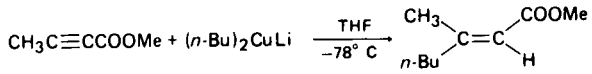
$$\mathrm{>C{=}C(B)\text{—} + \text{—}\overset{-}{C}COOR \longrightarrow B\text{—}CH\text{—}\overset{|}{\underset{|}{C}}\text{—}CCOOR} \qquad (460)$$

Conjugate additions of Grignard reagents to α,β-unsaturated esters, usually in the presence of copper(I) salts, is one of the most versatile methods for synthesizing β-substituted esters (equation 461)[1158]. In a recent report, bis-Grignard reagents have been found to react with two molecules of diethyl isopropylidenemalonate (equation 462)[1159].

$$\mathrm{R^1MgX + R^2R^3C{=}C(COOEt)_2 \longrightarrow R^2R^3R^1CH(COOEt)_2} \qquad (461)$$

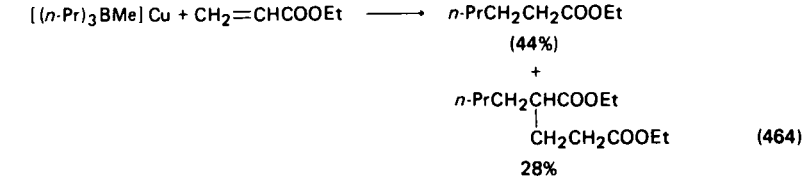
$$\mathrm{2\ Me_2C{=}C(COOEt)_2 + BrMg(CH_2)_5MgBr \xrightarrow[Et_2O]{CuI} (EtOOC)_2CHC(Me)_2\text{—}(CH_2)_5\text{—}C(Me)_2CH(COOEt)_2} \qquad (462)$$

Conjugate addition of lithium dialkylcuprates or polymeric copper complexes to α,β-acetylenic esters can be used to prepare α,β-ethylenic esters in good yields and with a high degree of stereoselectivity[1160]. For example, lithium di-*n*-butylcuprate reacts with methyl 2-butynoate to give a 97 : 3 ratio of the *E* and *Z* isomers of methyl 3-methyl-2-heptenoate in 86% overall yield (equation 463)[1160]. Addition of copper allenes to methyl acetylenecarboxylate gives methyl esters of 2,4,5-heptatrienoic acid[1161].



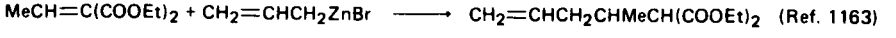
(463)

Although α,β-ethylenic esters which do not have a second electron-withdrawing substituent at the α-position tend to react sluggishly with organocopper reagents, certain cuprous methyltrialkylborates have been found to add to ethyl acrylate (equation 464)[1162].



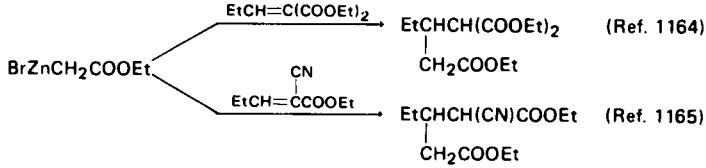
(464)

Allylzinc bromide participates in conjugate addition reactions with alkylidene malonates to produce unsaturated malonic esters (equation 465)[1163]. The Refor-



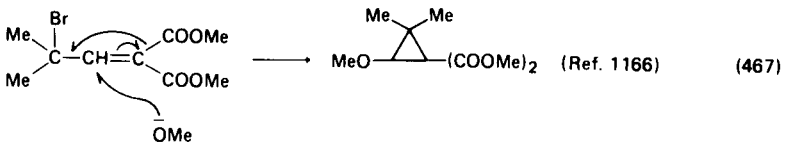
(465)

matsky reagent derived from ethyl bromoacetate adds to alkylidene malonates[1164] and alkylidenecyanoacetates[1165] (equation 466).



(466)

Nearly quantitative yields of methyl esters of 2,2,3-trisubstituted cyclopropanecarboxylic acids can be obtained as shown in equation (467)[1166].



(467)

9. *Claisen condensations*

The utility of the Claisen and Dieckmann reactions as methods for the synthesis of acyclic and cyclic β-keto esters is universally recognized. Both reactions have been reviewed[1167–1169].

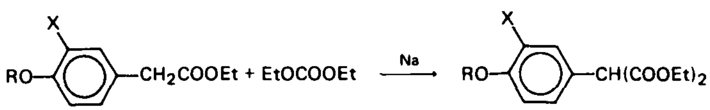
Simple Claisen condensations involve self-condensations of esters in the presence of a suitable basic reagent to afford β-keto esters (equation 468). When the ester to

$$R^1R^2CHCOOR^3 \overset{B^-}{\rightleftharpoons} R^1R^2\bar{C}COOR^3 \overset{R^1R^2CHCOOR^3}{\rightleftharpoons} R^1R^2\underset{\displaystyle COOR^3}{C}COCHR^1R^2 \qquad (468)$$

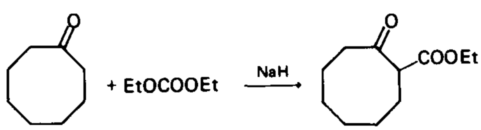
be employed has only one α-hydrogen the reaction proceeds poorly, because the desired β-keto ester lacks an ionizable methylene or methine hydrogen. Among the various basic reagents which have been employed in attempts to overcome this problem, potassium hydride now appears to be the most satisfactory and convenient for effecting self-condensation of α,α-disubstituted esters[1170].

Crossed Claisen condensations take two common forms, which can be used for the preparation of substituted malonic esters and β-keto esters, respectively. Thus, condensation of an ester possessing α-hydrogens with an oxalate or carbonate ester can afford substituted malonates. When a ketone is employed as the active hydrogen component with oxalates and/or carbonates, the product is a β-keto ester. These two procedures are especially valuable for preparing substituted malonic esters which cannot be synthesized by direct alkylation, and for synthesizing cyclic β-keto esters which cannot be obtained by Dieckmann reactions. These applications are illustrated in equations (469)–(471). Diethyl carbonate can also be used for introduction of a carboethoxy group into other types of active hydrogen substrates such as 2,6-lutidine[1174].

$$PhCH_2COOEt + (COOEt)_2 \xrightarrow[2.\ \Delta,\ -CO]{1.\ NaOEt} PhCH(COOEt)_2 \qquad \text{(Ref. 1171)} \qquad (469)$$



(Ref. 1172) (470)



(Ref. 1173) (471)

C. Esters by Free-radical Processes

1. *Radical additions and substitution reactions*

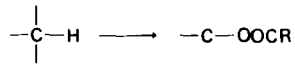
Carboalkoxylalkyl (–C–COOR) residues can be introduced into unsaturated substrates by means of the same type of radical-addition processes (equation 472)

$$R^1CH{=}CH_2 + -\overset{H}{\underset{|}{\overset{|}{C}}}COOR^2 \xrightarrow[\text{initiator}]{\text{radical}} R^1CH_2CH_2-\underset{|}{\overset{|}{C}}COOR^2 \qquad (472)$$

which have been outlined for introduction of carboxyalkyl residues (Section II.C). Direct aromatic substitution by carboalkoxyalkyl radicals is encountered less frequently than radical additions to unsaturated systems.

2. *Acyloxylation reactions*

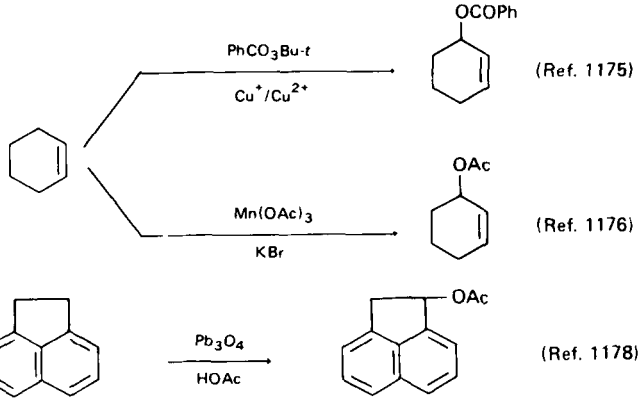
Acyloxylation can involve direct substitution of an acyloxy (RCOO·) function for a hydrogen attached to carbon (equation 473). These reactions often occur in



(473)

good yields when the hydrogen to be replaced is allylic, benzylic, or adjacent to a carbonyl, ether or thioether function. Reagents which furnish the acyloxy group include peroxy esters in the presence of transition-metal ions, carboxylic acids in the presence of hydroperoxides or dialkyl peroxides, peroxy acids, diacyl and diaroyl peroxides, and metal salts such as lead(IV) acetate, mercury(II) acetate, thallium(III) acetate and palladium(II) acetate.

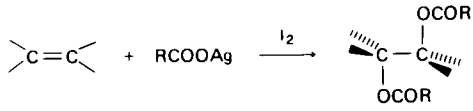
Acyloxylations at carbon by means of peroxides and metal salts have been reviewed recently[1175-1177]. Reactions (474) and (475) are representative of this



synthetic approach. A recent report claims high yields of phenylacetates from acetoxylation of substituted benzenes with palladium(II) acetate[1179]. The acetoxy group is introduced *meta* to most substituents. Lead(IV) trifluoroacetate has been used for trifluoroacetoxylation of aromatic substrates[1180,1181]. With compounds containing a trimethylsilyl group, introduction of the acyloxy group occurs by displacement of the trimethylsilyl moiety[1179]. Benzoyloxylation at the 5-position of certain pyrimidines by means of benzoyl peroxide has been reported[1182]. Substitutive acetoxylation of vinyl carbon has been accomplished using lead(II) acetate[1183].

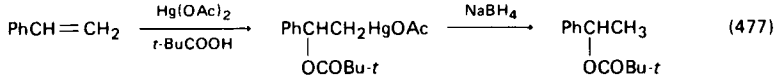
Esters can also be synthesized by acyloxylation reactions in which introduction of the RCOO– group is effected by addition to the multiple bond of unsaturated substrate rather than by substitution at an allylic position. Unlike the substitutive acyloxylations, these reactions do not necessarily involve free radicals. The Prevost reaction[1184-1186], in which an olefin is allowed to react with two equivalents of a

silver carboxylate in the presence of an equivalent of iodine (equation 476), represents an example of such a reaction. Thallium(I) carboxylates in the presence



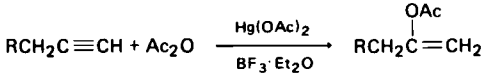
(476)

of iodine behave similarly to produce β-iodoalkyl carboxylates[1187]. Mercury(II) acetate adds to olefins to form acyloxy mercuriacetates, which can then be reduced with sodium borohydride to provide the desired ester (equation 477)[1188]. Re-



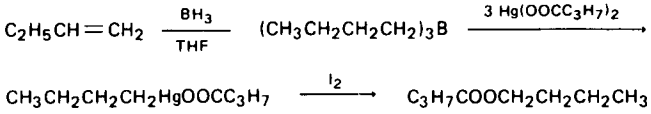
(477)

action of acetylenes with acetic anhydride in the presence of boron trifluoride etherate and a catalytic amount of mercury(II) acetate affords alkenyl acetates in good yields (equation 478)[1189].



(478)

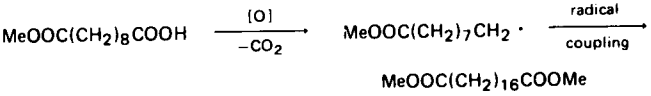
Although the acyloxylations of olefins described above involve Markownikoff addition of the carboxylic acid to alkenes and alkynes, a new procedure has been developed for anti-Markownikoff esterification of olefins. This method involves hydroboration of the alkene, followed by reaction of the resulting trialkylborane with a mercuric carboxylate to form a primary alkylmercuric carboxylate, which is then treated with iodine to give a primary ester. The synthesis of *n*-butyl butyrate from 1-butene illustrates the reaction scheme (equation 479)[1190].



(479)

3. *Anodic dimerization*

Kolbe electrolysis of half-esters of dicarboxylic acids is a useful route to symmetrical dicarboxylic acid esters (equation 480). This reaction, which has been



(480)

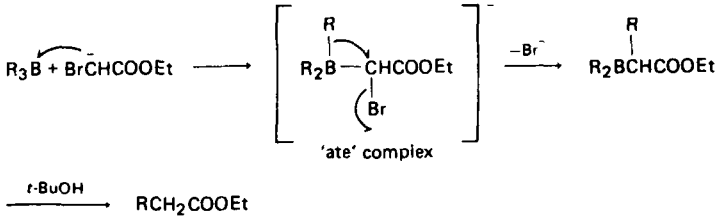
discussed in detail elsewhere[1191-1193], involves electrochemical oxidation of half-esters at a platinum anode to generate ω-carboalkoxy radicals, which then undergo dimerization to form the desired diesters. Related reactions involving radical intermediates formed in electrolytic oxidations of acids have been reviewed[1194].

D. Miscellaneous Ester Syntheses

1. From organoboranes

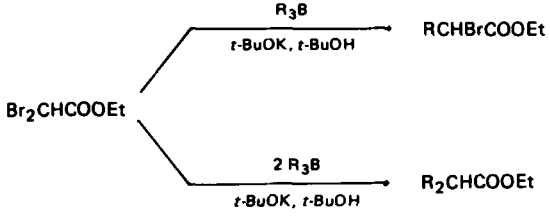
Organoboranes[1195] can be employed in several general types of ester syntheses. In each of these methods the boranes react with various classes of esters to effect elaboration of the original ester structure.

Reactions of α-bromo esters with trialkylboranes in the presence of potassium *t*-butoxide in *t*-butyl alcohol results in introduction of an alkyl group in place of the α-bromine (equation 481)[1196]. This α-alkylation presumably involves initial

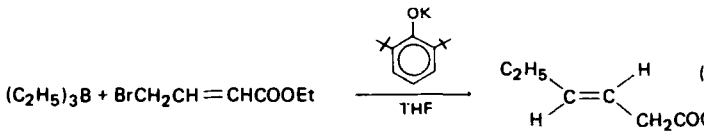


(481)

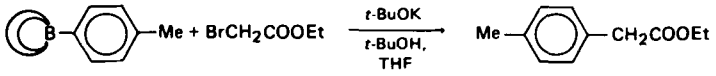
formation of an 'ate' complex from the α-bromo carbanion of the ester and the trialkylborane. Migration of an alkyl group from boron to carbon is accompanied by loss of bromide ion to give a new trialkylborane, in which one of the alkyl residues is an α-alkylacetate moiety. Cleavage of the α-carbon–boron bond is then effected by *t*-butyl alcohol to afford α-alkylacetates. Improvements in the original procedure include the use of potassium 2,6-di-*t*-butylphenoxide[1197,1198] as the basic reagent and β-alkyl- and β-aryl-9-borabicyclo[3.3.1]nonanes as the source of the alkyl or aryl group[1199]. If dihalo esters are used it is possible to prepare α-bromo esters or α,α-dialkyl esters by varying the amount of organoboranes (equation 482)[1200]. Equations (483) and (484) illustrate several additional appli-



(482)



(483)

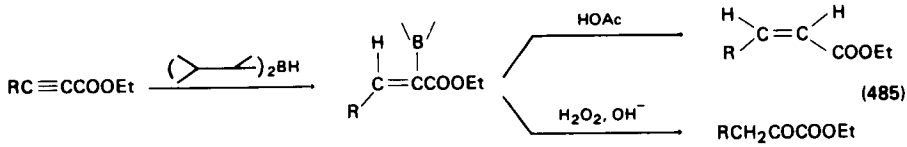


(484)

cations of this α-alkylation method to the synthesis of esters. The organoborane alkylation procedure complements other methods such as the malonic ester syn-

thesis and alkylation of α-anions in that it allows facile introduction of highly-branched alkyl substituents as well as aryl groups.

Stereoselective synthesis of (*Z*)-α, -unsaturated esters can be accomplished by addition of disiamylborane to α,β-acetylenic esters followed by protonolysis. When the adduct is oxidized with alkaline hydrogen peroxide, α-keto esters are produced (equation 485)[1203].

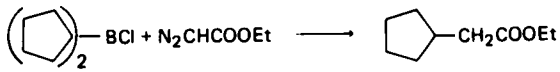


(485)

Trialkylboranes react with ethyl diazoacetate to provide α-substituted acetates (equation 486)[1204]. Introduction of bulky alkyl groups is accomplished more

$$R_3B + N_2CHCOOEt \xrightarrow[2.\ H_2O]{1.\ THF} RCH_2COOEt \qquad (486)$$

efficiently with dialkylchloroboranes (equation 487)[1205]. α-Bromo esters can be prepared by reaction of trialkylboranes with ethyl diazoacetate followed by addition of *N*-bromosuccinimide to the reaction mixture (equation 488)[1206].

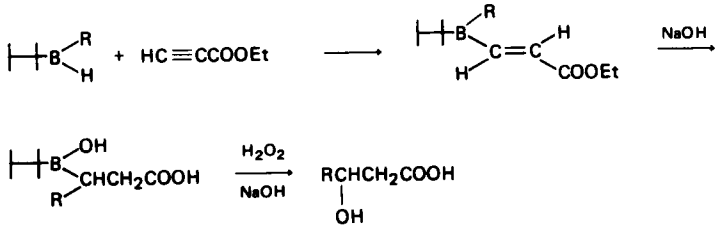


(487)

$$N_2CHCOOEt \xrightarrow[2.\ NBS]{1.\ (C_2H_5)_3B} C_2H_5CHBrCOOEt \qquad (488)$$

Trialkynylboranes also react with ethyl diazoacetate to form β,γ-acetylenic esters in excellent yields[1207].

Treatment of ethyl propiolate with thexylmonoalkylboranes leads to initial hydroboration of the triple bond. Subsequent reaction of the resulting alkenylborane with hydroxide ion leads to alkyl-group migration. Hydrolysis with aqueous hydrogen peroxide then affords β-hydroxy acids (equation 489)[1208].



(489)

2. *From acetylenes*

Alkali-metal salts of ethoxyacetylene can be alkylated with alkyl halides and the 1-ethoxyethynyl portion of the resulting acetylene then converted to a carboethoxymethylene group upon mercuric oxide-catalysed hydration of the triple bond (equation 490)[1209]. Thus, ethoxyacetylene serves as a two-carbon homolo-

$$EtOC{\equiv}CNa + BuBr \xrightarrow{NH_3} BuC{\equiv}COEt \xrightarrow[H_2SO_4]{HgO} BuCH_2COOEt \qquad (490)$$

gating agent in ester preparation. More recently[1210], it has been found that 1-ethoxyvinyl esters, obtained by mercuric ion-catalysed addition of carboxylic acids to ethoxyacetylene, can be converted to β-keto esters upon treatment with zinc salts (equation 491). This reaction scheme is equivalent to acylation and

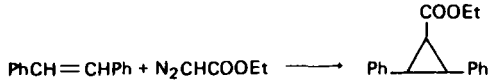
$$EtOC{\equiv}CH + RCOOH \xrightarrow{Hg^{2+}} RCOOC(OEt){=}CH_2 \xrightarrow[2.\ H_3O^+]{1.\ Zn^{2+}} RCOCH_2COOEt \qquad (491)$$

hydration of ethoxyacetylene. Terminal acetylenes have recently been converted to α-keto esters by ozonization in methanol (equation 492). 1-Bromoacetylenes undergo a similar conversion when potassium iodide is added to the reaction mixture after treatment with ozone[618].

$$RC{\equiv}CH \xrightarrow[2.\ SOCl_2]{1.\ O_3,\ MeOH} RCOCOOMe \qquad (492)$$

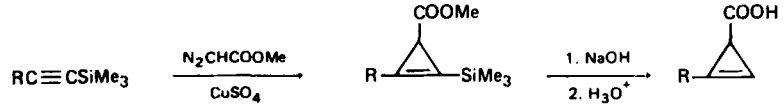
3. *From diazo esters*

The utility of ethyl diazoacetate in ester synthesis was demonstrated earlier in reactions involving organoboranes. In addition to these reactions, ethyl diazoacetate can be employed in the preparation of cyclopropanecarboxylic acids and esters as shown in the reaction with stilbene (equation 493)[1211]. Cyclopropenecarboxylic



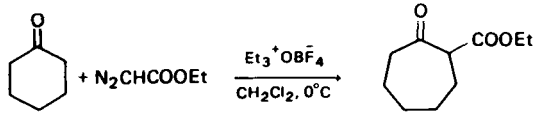
(493)

acids can be prepared in an anologous manner from 1-trimethylsilylacetylenes (equation 494)[1212]. When ethyl diazoacetate is allowed to react with both cyclic



(494)

and acyclic ketones in the presence of triethyloxonium fluoroborate, ring expansion or one-carbon homologation takes place to form β-keto esters (equation 495)[1213]. The preparations and reactions of diazo esters have been reviewed[1214,1215].



(495)

IV. SYNTHESIS OF ACID ANHYDRIDES

The most frequently employed methods for synthesizing carboxylic acid anhydrides involve dehydrative coupling of acids, acylation of carboxylate salts with acyl halides, reactions of acids with dissimilar anhydrides in a type of anhydride interchange, and reactions of acids with ketene. Cyclic anhydrides of various types are often prepared by Diels Alder reactions of maleic anhydride with dienes[11,1216]. All of these methods, along with several more specialized procedures have been discussed in recent reviews[1217,1218]. The synthetic methods described in this section represent newer procedures in the areas of dehydrative coupling of carboxylic acids and acylation of carboxylate salts.

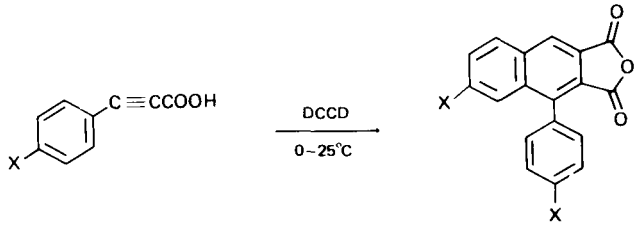
A. Dehydrative Coupling of Carboxylic Acids

These reactions are represented by the general equation (496) in which two molecules of acid react to form an anhydride and a molecule of water. Actually

$$2\ RCOOH \longrightarrow (RCO)_2O + H_2O \qquad (496)$$

such dehydrations are used mainly to prepare cyclic anhydrides from dibasic acids. Acyclic acids seldom undergo purely thermal anhydride formation. Consequently, acyclic anhydrides are prepared through reactions of this type by adding an appropriate reagent which reacts with the free carboxyl group of the acid to produce an activated derivative. The activated acid is then attacked by the weakly nucleophilic oxygen of a free acid molecule to produce an anhydride. This approach allows the conversion of carboxylic acids into anhydrides to be accomplished under mild conditions.

Various carboxylic acids yield symmetrical anhydrides upon treatment with dicyclohexylcarbodiimide (DCCD)[1219,1220] or ethoxyacetylene[1221-1223]. It has been found that insoluble polystyrene polymer containing carbodiimide residues can be employed to effect anhydride formation from acetic, stearic and glutaric acids[1224]. Phenylpropiolic acids undergo an unusual cyclodimerization in the presence of DCCD to form 1-phenylnaphthalene-2,3-dicarboxylic anhydrides (equation 497)[1225]. Ynamines are claimed to be superior to DCCD and ethoxy-



(497)

acetylene for dehydrative coupling of acids[1226]. Other reagents which are satisfactory for dehydration of acids include iodosobenzene[1227], trisdimethylamino phosphine[1228], chlorotrisdimethylaminophosphonium perchlorate[1229], triphenylphosphine dibromide[1230], cyanogen bromide[1231] and phenylisocyanate[1232].

Reaction of mono- and dicarboxylic acids with thionyl chloride has been reinvestigated as a method for preparing symmetrical anhydrides[1233]. In contrast to earlier reports, anhydrides were found to form readily without the need for

added pyridine. Thionyl bromide has been employed as a dehydrating agent to produce cyclic anhydrides[1234].

B. Acylation of Carboxylate Salts

This classical procedure for synthesizing anhydrides consists of treatment of alkali metal, silver or thallium(I) carboxylates with an acyl chloride (equation 498).

$$R^1COOM + R^2COCl \longrightarrow R^1COOCOR^2 + MCl \quad (498)$$

This method has a decided advantage over dehydrative coupling in that unsymmetrical anhydrides are readily synthesized.

A convenient method for the preparation of symmetrical aromatic acid anhydrides consists of treatment of an aromatic acid chloride with aqueous sodium bicarbonate containing catalytic amounts of pyridine (equation 499)[1235].

$$ArCOCl \xrightarrow[\text{pyridine, } 20^\circ C]{NaHCO_3} ArCOOCOAr \quad (499)$$

Reaction of silver or mercury(I) carboxylates with *N,N'*-dicyclohexylthiourea at room temperature in acetone, chloroform or acetonitrile, constitutes a useful method for the preparation of anhydrides from acid salts (equation 500)[1236]. This

$$2\ RCOOAg + C_6H_{11}NHC(=S)NHC_6H_{11} \longrightarrow RCOOCOR + Ag_2S + C_6H_{11}NHC(=O)NHC_6H_{11} \quad (500)$$

procedure bears a resemblance to an older method in which silver benzoate was converted to benzoic anhydride by means of carbon disulphide[1237].

α-Oxo sulphoxides, obtained by oxidation of thiol esters with *N*-bromosuccinimide, react with sodium salts of carboxylic acids to afford anhydrides (equation 501)[1238].

$$R^1C(=O)S(=O)R^2 + R^3COONa \longrightarrow R^1COOCOR^3 \quad (501)$$

V. SYNTHESIS OF ACYL HALIDES

Preparations of acyl halides have been reviewed in a previous volume of this series published in 1972[1239]. For the sake of consistency we have followed, where appropriate, the general format of this earlier review in presenting more recent developments in the field of acyl halide synthesis.

A. From Carboxylic Acids and Anhydrides

In addition to the common halogenating agents such as thionyl chloride, phosphorus halides, carbonyl halides and sulphonyl halides, several new reagents have been found to be effective for converting acids and/or anhydrides into acyl halides.

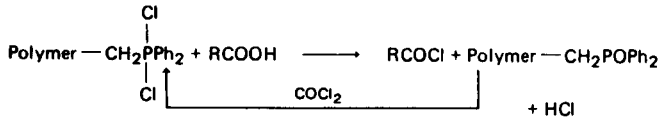
Acyl chlorides can be prepared in good yields under mild conditions by reaction of carboxylic acids with trialkyl- or triarylphosphines in carbon tetrachloride (equation 502). This procedure is very attractive for acid-sensitive carboxylic acids,

$$RCOOH + Ph_3P + CCl_4 \longrightarrow RCOCl + Ph_3PO + CHCl_3 \quad (502)$$

as no hydrogen chloride is produced during the reaction[1240]. However, one disadvantage is the bothersome separation of triphenylphosphine oxide from the desired acyl chloride. This can be avoided by employing a polymer-supported triphenylphosphine[1241]. With such reagents the phosphine oxide function remains attached to the polymer framework, and can be removed by filtration (equation 503).

$$Polymer-PPh_2 + RCOOH + CCl_4 \longrightarrow RCOCl + Polymer-POPh_2 + CHCl_3 \quad (503)$$

A procedure related to the polymer-supported triphenylphosphine method utilizes trisubstituted phosphine dichloride groupings chemically bonded to cross-linked polystyrene beads (equation 504). The recovered polymeric phosphine

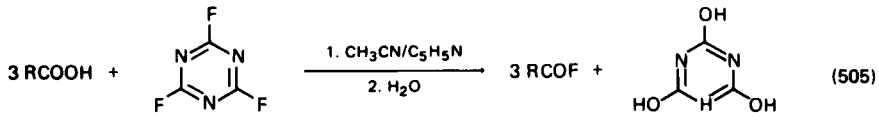


(504)

oxides can be reconverted to the original phosphine dichlorides by treatment with phosgene[1242].

Phosgene continues to be a useful and economical reagent for large-scale production of acyl chlorides from both acids and anhydrides. Recent studies have shown that phosgene functions best when used in the presence of nitrogen-containing catalysts such as imidazole[1243], DMF[1244] and caprolactam[1245].

Several less traditional reagents have been used for the conversion of acids to acyl chlorides. These include sulphur monochloride[1246], a mixture of sulphur dichloride and chlorine[1247] and phosphosalicylic halides[1248]. Reaction of carboxylic acids with hydrogen chloride and ethyl isocyanate in ethereal solution at room temperature affords acid chlorides in good yields.



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Acyl bromides can be prepared from carboxylic acids by reaction with thionyl bromide[1249] or by adding bromine to a mixture of the acid and phosphorus tribromide[1250].

Several new methods for direct preparation of acyl fluorides have appeared recently. Cyanuric fluoride is a mild reagent suitable for the preparation of acyl fluorides from acids containing unsaturation, hydroxyl groups or aromatic rings[1251]. Dialkylaminosulphur trifluorides[1252] and selenium tetrafluoride[1253] can be used to prepare acyl fluorides from acids. The latter reagent also reacts with anhydrides to give acyl fluorides, while the former reacts with acyl chlorides to afford fluorides by halogen exchange[1254]. Reaction of benzoyl chloride with hydrogen fluoride to give benzoyl fluoride is typical of standard exchange procedures for acyl fluoride preparation[1255].

Although thionyl chloride is often the reagent of choice for preparing acyl chlorides from carboxylic acids, several undesirable side-reactions can take place

depending upon reaction conditions and the method of product isolation. For example, thionyl chloride in the presence of catalytic amounts of pyridine has been shown to afford mainly α-chloro-α-chlorosulphenylacyl chlorides (equation 506)[1256,1257]. In a related reaction, chlorosulphonylalkanoyl chlorides are pro-

$$RCH_2COOH + SOCl_2 \xrightarrow{C_5H_5N} \begin{matrix} Cl \\ | \\ RCCOCl \\ | \\ SCl \end{matrix} \qquad (506)$$

duced in good yields on treatment of alkanoic acids with chlorosulphonic acid or a mixture of sulphur trioxide and phosphorus oxychloride (equation 507)[1258].

$$R^1R^2CHCOOH + SO_3 + POCl_3 \longrightarrow R^1R^2C\begin{matrix} COCl \\ SO_2Cl \end{matrix} \qquad (507)$$

Previous reports that aromatic acids which contain electron-withdrawing substituents cannot be satisfactorily converted to acyl chlorides by means of thionyl chloride have been disproved by the synthesis of 4-nitrobenzoyl chloride[1259]. Reinvestigation of the reaction of phenylmalonic acid with thionyl chloride has revealed that chlorocarbonyl ketenes can be prepared by this reaction if the crude product is refluxed in toluene or xylene prior to final distillation (equation 508)[1260].

$$RCH(COOH)_2 \xrightarrow{SOCl_2} RCH(COCl)_2 \xrightarrow[\Delta]{-HCl} RC\begin{matrix} =C=O \\ COCl \end{matrix} \qquad (508)$$

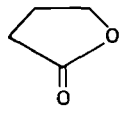
B. From Esters

Esters and lactones can be cleaved to form acyl halides by treatment with triphenylphosphine dihalides (equation 509) or a mixture of triphenylphosphine

$$R^1COOR^2 + Ph_3PX_2 \longrightarrow R^1COX + R^2X + Ph_3PO \qquad (509)$$

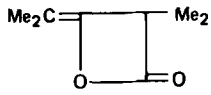
dichloride and boron trifluoride[1261,1262]. Esters of halogenated acids are cleaved in refluxing acetonitrile, whereas unsubstituted esters require higher temperature. Phenyl esters do not react with these reagents.

Thionyl chloride and zinc chloride can be used to produce γ-chlorobutryoyl chloride from butyrolactone (equation 510)[1263]. 3-Hydroxy-2,2,4,3-pentenoic



$$+ SOCl_2 + ZnCl_2 \longrightarrow Cl(CH_2)_3COCl \qquad (510)$$

acid β-lactone is similarly converted to 2,2,4-trimethyl-3-oxovaleryl chloride with zinc chloride and anhydrous hydrogen chloride (equation 511)[1264].



$$\xrightarrow[ZnCl_2]{HCl} Me_2CHCOCMe_2COCl \qquad (511)$$

Trimethylsilyl esters are converted to acid chlorides by thionyl chloride[1265]. Isopropenyl esters afford acyl fluorides on treatment with hydrogen fluoride[1266].

C. From Trihalides

Trichloromethyl arenes can serve as useful precursors to aroyl chlorides (equation 512). Several new methods are available for accomplishing such conversions.

$$ArCCl_3 \longrightarrow ArCOCl \qquad (512)$$

For example, benzotrichlorides react with sulphur dioxide above 150°C to form benzoyl chlorides and thionyl chloride[1267]. Lewis-acid catalysts allow these reactions to proceed at lower temperatures. Bis(trichloromethyl)arenes are converted to diacid chlorides under these reaction conditions. Trichloromethylarenes also yield aroyl chlorides on treatment with sulphur trioxide at 25–50°C[1268]. Toluene, benzyl chloride and benzal chloride, as well as a number of their substituted derivatives, react with thionyl chloride above 200°C to yield benzoyl chlorides.

Conversion of aliphatic trichlorides into acyl chlorides is encountered infrequently. However, a new synthesis of *t*-butoxycarbonyl fluoride involves initial transformation of fluorotrichloromethane into carbonyl chloride–fluoride, which is subsequently reacted with *t*-butyl alcohol to give the carbonyl fluoride (equation 513)[1270].

$$Cl_3CF \xrightarrow[SO_3]{H_2SO_4} ClCOF \xrightarrow[Et_3N]{t\text{-BuOH}} t\text{-BuOCOF} \qquad (513)$$

D. By Carbonylation

Benzylic halides undergo carbonylation with carbon monoxide in the presence of chlorocarbonyl-bis(triphenylphosphine)rhodium to form phenylacetyl halides (equation 514)[1271,1272]. Carbonylation of allylic halides affords unsaturated acyl

$$ArCH_2X + CO \xrightarrow[150°C,\ 150\ kg/cm^2]{Ph_3P(CO)Cl} ArCH_2COX \qquad (514)$$

halides with carbon monoxide over a palladium or rhodium catalyst at 100–150°C and 3000 psi[1273].

Olefinic substrates can be carbonylated in the presence of hydrogen chloride using ligand-stablized palladium(II), tin(II) or germanium(II) chlorides. Thus, reaction of 1-heptene under these conditions gives octanoyl chloride (equation 515)[1274]. Dinuclear metal carbonyl compounds such as cobalt octacarbonyl

$$CH_3(CH_2)_4CH{=}CH_2 + CO + HCl \xrightarrow[90°C,\ 3000\ psi]{PdCl_2(PPh_3)_2} CH_3(CH_2)_4CH_2CH_2COCl \qquad (515)$$

catalysed the carbonylation of olefins in carbon tetrachloride solution to give 2-alkyl-4,4,4-trichlorobutanoyl chlorides[1275,1276]. Here again, reaction conditions are rather stringent, with temperatures ranging from 50–130°C and carbon monoxide pressures of 60–200 atm.

In a reaction which may be regarded as analogous to carbonylation, phosgene undergoes 1,2-addition with alkynes in ether at low temperature to produce

3-alkylthio-3-chloroacryloyl chlorides in moderate to good yields (equation 516)[1277].

$$R^1SC{\equiv}CR^2 + COCl_2 \longrightarrow \begin{matrix} R^1S & & R^2 \\ & C{=}C & \\ Cl & & COCl \end{matrix} \qquad (516)$$

Benzoyl fluoride and terephtaloyl fluoride can be prepared from arenesulphonyl fluorides, or from arenesulphonyl chlorides and sodium fluoride, by treatment with carbon monoxide in the presence of palladium (equation 517)[1278].

$$ArSO_2F + CO \xrightarrow[>200^\circ C,\ 100\ atm]{Pd} ArCOF + SO_2 \qquad (517)$$

E. Miscellaneous Methods

Aryl aldehydes are chlorinated to form aroyl chlorides by means of sulphur monochloride in the presence of catalytic amounts of DMF (equation 518)[1279].

$$ArCHO + S_2Cl_2 \xrightarrow[40-90^\circ C]{DMF} ArCOCl \qquad (518)$$

Δ^2-Alkenoic acid chlorides are available by allowing ketene to react with boron trichloride adducts of aldehydes and ketones (equation 519)[1280].

$$R^1COR^2 + CH_2{=}C{=}O \xrightarrow[ether]{BCl_3} R^1R^2C{=}CHCOCl \qquad (519)$$

VI. SYNTHESIS OF AMIDES

Most of the important methods of amide synthesis reported in the chemical literature through 1971 have been reviewed[1281-1284]. Consequently, emphasis here is directed toward procedures which have appeared since then.

A. Amides by Acylation Reactions

Acylations of ammonia and amines with carboxylic acids and acid derivatives constitute the most important class of reactions leading to amides (equation 520).

$$R^1COX + HN\!\!<\!\!\!> \longrightarrow R^1CON\!\!<\!\!\!> + HX$$

$$X = OH,\ halogen,\ R^2COO,\ R^2O \qquad (520)$$

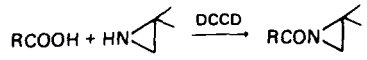
Acyl halides and anhydrides are used most frequently because they are more reactive toward nitrogen nucleophiles than are acids and esters. The following syntheses are categorized in terms of the type of acylating reagent employed.

1. Acylations with carboxylic acids

Prior to the discovery of reagents which can catalyse the acylation of amines with free carboxylic acids, amide formation was usually accomplished by thermo-

lysis of ammonium carboxylates. Such conditions are often unsatisfactory, as in the formation of peptide bonds from stereochemically labile amino acids. A review of coupling reagents which activate the carboxyl group of free acids toward reactions with amine nucleophiles has appeared recently[1285].

Dicyclohexylcarbodiimide (DCCD) continues to be among the most popular and useful reagents for amide formation from free acids. For example, *N*-acylaziridines, which serve as useful intermediates for the preparation of 2-oxazolines, can be prepared using DCCD (equation 521)[1286]. Similarly, *N*-hydroxy- and *N*-alkoxy-



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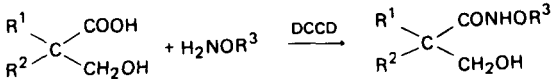
3-hydroxypropanamides are obtained by reaction of DCCD or diisopropylcarbodiimide with 3-hydroxypropanoic acids and hydroxylamine or its *O*-alkyl derivatives (equation 522)[1287].



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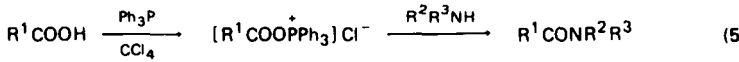
Several organophosphorus reagents have been employed in amide formation. Reaction of carboxylic acids with the complex formed from triphenylphosphine and carbon tetrachloride affords triphenylacyloxyphosphonium chlorides, which in turn react with various primary and secondary amines to produce the desired amides (equation 523)[1288]. Trisdimethylamino phosphine can be used in place of



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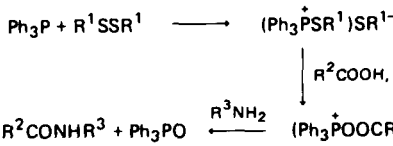
triphenylphosphine[1228]. As mentioned earlier[1228], if the amine is omitted, anhydrides are produced in reactions involving these phosphine reagents. Triphenylphosphite in combination with imidazole promotes formation of steroidal amides from the free acids[1289,1290]. Amides can also be prepared from carboxylic acids and amines using phosphorus acid or its mono-, di- or triesters in the presence of pyridine and iodine or bromine as an oxidizing agent[948,949]. This procedure is also useful for esterification of carboxylic acids if alcohols are added to the reaction mixture in place of amines.

Treatment of carboxylic acids or *N*-protected amino acids with simple amines or free amino-acid esters in the presence of a mixture consisting of triphenylphosphine, dichlorodiphenyl disulphide, triethylamine and copper(II) chloride affords simple amides or peptides in high yields (equation 524)[1291]. The reaction is



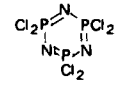
(524)

assumed to proceed through initial formation of a phosphonium salt via reaction of triphenylphosphine with the disulphide. This salt then reacts with the carboxylic acid to form a phosphonium carboxylate, which in turn effects acylation of the

amine or amino-acid ester to produce the observed amide or peptide. The sulphide by-product is removed as its copper(II) salt. Amides and peptides are available in good yields from carboxylic acids and amines using diethyl phosphorocyanidate as the coupling agent (equation 525)[1292]. Acyl cyanides appear to be the reactive

$$R^1COOH + R^2R^3NH \xrightarrow[Et_3N]{NCP(O)(OEt)_2} R^1CONR^2R^3 \qquad (525)$$

intermediates in these acylations. Hexachlorocyclotriphosphatriazine (equation 526)[1293] and triphenylphosphonium triflate[950] have also been used to effect



$$R^1COOH + R^2NH_2 \longrightarrow R^1CONHR^2 \qquad (526)$$

amide formation. The latter reagent is also an efficient promoter of ester formation.

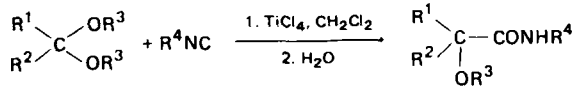
Silicon tetrachloride has attracted considerable attention as a coupling reagent for amide formation[1294]. Condensations of *N*-protected amino acids with amino-acid esters proceed best with this reagent if the acid is first converted to the tetraacyloxysilane (equation 527)[1295].

$$R^1NHCH_2COOH \xrightarrow[pyridine]{SiCl_4} (R^1NHCH_2COO)_4Si \xrightarrow{H_2NCH_2COOR^2} R^1NHCH_2CONHCH_2COOR^2 \qquad (527)$$

Carboxylic acids and amines react at room temperature in the presence of stoichiometric amounts of titanium(IV) chloride to form amides as shown in the production of *N*-ethylformamide (equation 528)[1296]. Titanium(IV) chloride also

$$2\,HCOOH + 6\,EtNH_2 + TiCl_4 \longrightarrow 2\,HCONHEt + 4\,EtNH_3Cl + TiO_2 \qquad (528)$$

catalyses the formation of 2-alkoxyalkanamides from acetals and isocyanides by activating the acetals toward nucleophilic attack by the isocyanides (equation 529)[1297].



$$\xrightarrow[2.\ H_2O]{1.\ TiCl_4,\ CH_2Cl_2} \qquad (529)$$

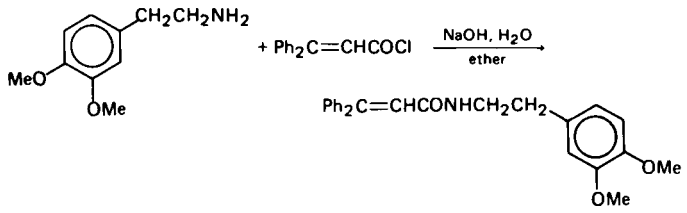
Attempts to develop satisfactory boron reagents for amide and peptide syntheses led to the discovery that trimethoxyborane in the presence of catalytic amounts of *p*-toluenesulphonic acid was suitable for the preparation of simple amides, but unsatisfactory for the synthesis of peptides[1298]. Recently, boron trifluoride etherate has been found to function as an effective reagent for amidation of carboxylic acids. Reactions are conducted by simply refluxing an acid and amine in benzene or toluene in the presence of triethylamine[1299].

Several coupling reagents which are useful for esterification of acids can also be employed for amide synthesis if an amine is used in place of an alcohol or phenol. *N*-Methyl-2-halopyridinium iodides[958], β-trichloromethyl-β-propiolactone[953], *N,N'*-carbonyldiimidazole[954] and certain allenic sulphonium salts[1300] fall into this category.

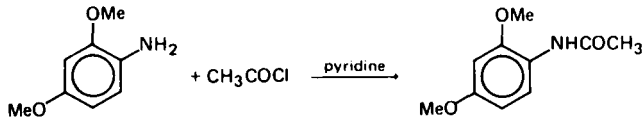
2. *Acylations with acyl halides*

Acylation of ammonia or primary and secondary amines with acid chlorides is probably the most frequently employed method of amide preparation. However, this route suffers from some marked disadvantages, especially with carboxylic acids which are sensitive to reagents required for their conversion to acyl halides.

General experimental procedures usually involve reaction of the acyl halide with an excess of an appropriate amine, or with a molar equivalent of the amine to be acylated, along with an excess of a tertiary amine or alkali metal hydroxide to absorb the acid formed during acylation. The reactions shown in equations (530)–(532) are representative of recent examples of amide formation from acyl



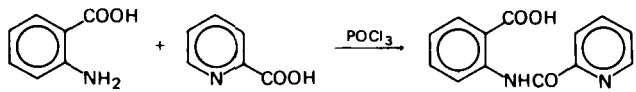
(Ref. 1301) (530)



(Ref. 1302) (531)

$$2\,CH_3NH_2 + (CH_3)_3CH(CH_2)_2COCl \xrightarrow{\text{ether}} (CH_3)_2CH(CH_2)_2CONHCH_3$$ (Ref. 1303) (532)

halides. An interesting example of amine acylation by an acid chloride is found in the synthesis of 2-picolinolylaminobenzoic acid, which is accomplished by dropwise addition of phosphorus oxychloride to a mixture of anthranilic acid and 2-picolinic acid in toluene (equation 533)[1304].



(533)

In some instances acylations can be accompanied by loss of a substituent other than hydrogen from the amino nitrogen. Thus, silyl-protected secondary amines lose the trialkylsilyl grouping upon treatment with acid chlorides (equation 534)[1305].

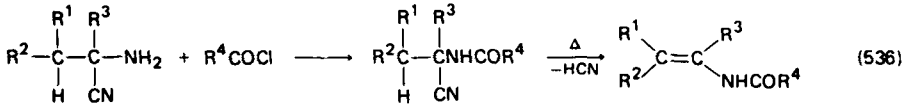
$$PhCH_2NMeSi(Et)_3 + CH_3COCl \xrightarrow{n\text{-hexane}} PhCH_2NMeCOCH_3 + Et_3SiCl$$ (534)

Reaction of tertiary methylamines with 2,2,2-trichloroethyl chloroformate affords the corresponding demethylated trichlorocarbamates in excellent yields (equation 535). The carbamates can subsequently be reduced with zinc in acetic

$$R^1R^2NCH_3 + Cl_3CCH_2OCOCl \xrightarrow{\text{benzene}} R^1R^2NCOOCH_2CCl_3 \xrightarrow[HOAc]{Zn} R^1R^2NH$$ (535)

acid or methanol to afford secondary amines. This procedure represents a convenient new method for amine demethylation[1306].

Enamides can be synthesized by acylation of 2-aminonitriles with acid chlorides followed by thermal dehydrocyanation of the resulting 2-acylaminonitriles (equation 536)[1307].



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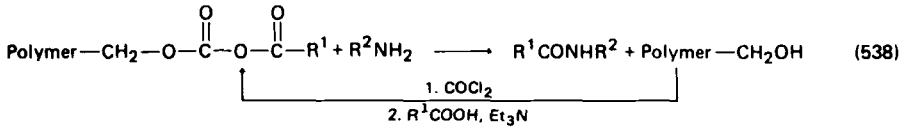
3. Acylations with anhydrides

Ammonolysis and aminolysis of carboxylic acid anhydrides are quite similar to acylations involving acid halides, Numerous examples of such reactions may be found in the cited review articles dealing with preparations of amides. Among the more interesting recent findings in this area of synthesis is the discovery that tertiary amines undergo dealkylative acylation with acetic anhydride at reflux (equation 537)[1308]. The alkyl groups expelled most easily are *t*-butyl, benzyl, α-phenylethyl, diphenylmethyl and trityl.

(537)

Polymeric anhydrides, prepared from chloromethylated polystyrene, react with aliphatic and aromatic primary amines to produce amides. The resulting hydroxymethylated polymer, can be reconverted to the polymeric anhydride by treatment with phosgene, followed by reaction with an appropriate carboxylic acid and triethylamine (equation 538)[1309].



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4. Acylations with esters

As would be anticipated, esters are less reactive acylating reagents than acyl halides and anhydrides. Phenyl formate, does however, react rapidly with primary aliphatic and aromatic amines to afford *N*-substituted formamides (equation 539)[1310]. D-Glucosamine is readily acylated by means of *p*-nitrophenyl esters in

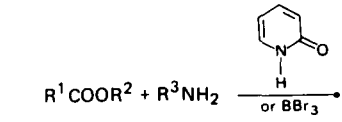
(539)

DMSO[1311]. Less reactive esters usually require catalysts in order to serve as useful acylating agents.

2-Pyridone has been shown to be effective in promoting reactions between various aliphatic amines and non-activated esters[1312]; more recently, boron tribromide has been used to effect amination of esters[1313] (equation 540).

1,1-Dicyanoethyl acetate, prepared from acetic anhydride and cyanide ion, is a useful activated ester, which reacts rapidly with amines to form *N*-substituted

acetamides in excellent yields (equation 541)[1314]. Another class of activated esters, 2-phenyl-3-(acyloximino)-3*H*-indoles, react readily with amines to give carboxamides (equation 542)[1315].



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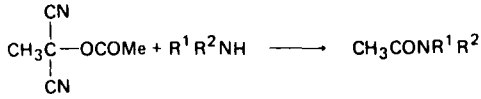

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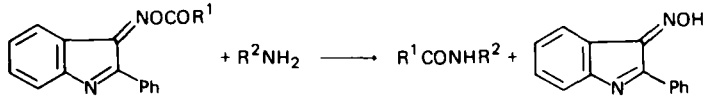
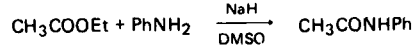


(542)

Conversion of amines to alkali-metal salts, which are then allowed to react with an appropriate ester to form amides, has been accomplished with lithium aluminium hydride[1316], *n*-butyllithium[1317] and sodium hydride[1318] (equations 543 and 544).



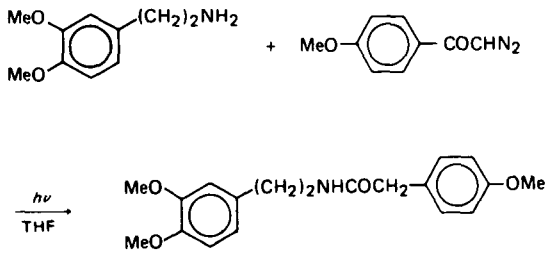
(543)

(544)

5. *Acylations with ketenes and isocyanates*

Ketene reacts smoothly with primary and secondary amines to form acetamides. Ketene acylations are used less frequently than those involving the more readily accessible acid halides and anhydrides. However, with acid-sensitive amines such acylations can be attractive. Reaction of β-methylallylamine with ketene is representative of amide formation[1319]. Acylations of amino alcohols with ketenes show a high degree of selectivity, giving rise to exclusive formation of *N*-acyl derivatives[1320]. Photolysis of mixtures of amines and diazo ketones provides a useful method of amide synthesis (equation 546). Photolytic decomposition of the diazo ketone produces a substituted ketene, which reacts with the amine[1321].

(545)



(546)

Isocyanates react with Grignard reagents (equation 547) and organolithium reagents to form amides[1322]. The required isocyanates can be prepared by Curtius reaction of acid chlorides with sodium azide. Amide formation is then accomplished by addition of the crude isocyanate to an ethereal solution of an appropriate lithium reagent (equation 548). The generality of this reaction scheme has been demonstrated with various acid chlorides and methyl-, *n*-butyl-, and phenyllithium[1323].

$$R^1N{=}C{=}O + R^2MgX \longrightarrow R^2CONHR^1 \tag{547}$$

$$R^1COCl \xrightarrow[\Delta]{1.\ NaN_3} R^1N{=}C{=}O \xrightarrow[2.\ H_3O^+]{1.\ R^2Li} R^1NHCOR^2 \tag{548}$$

Treatment of trimethylsilyl isocyanate or chloroacetyl isocyanate with Grignard reagents in dioxan at low temperature affords primary amides in good yields (equations 549 and 550). The trimethylsilyl group is cleaved during aqueous workup, while sodium methoxide is required to remove the chloroacetyl function[1324].

$$Me_3SiN{=}C{=}O \xrightarrow{R^1MgX} [Me_3SiNHCOR^1] \xrightarrow[NH_4Cl]{H_2O} R^1CONH_2 \tag{549}$$

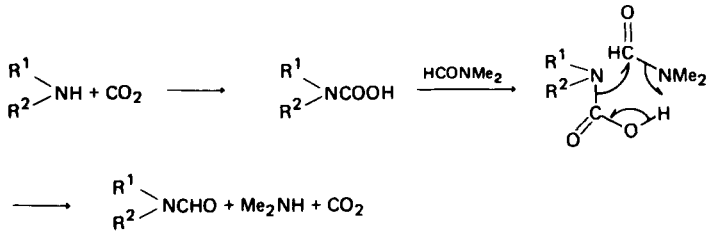
$$ClCH_2CON{=}C{=}O \xrightarrow{R^1MgX} [ClCH_2CONHCOR^1] \xrightarrow[MeOH]{MeONa} R^1CONH_2 \tag{550}$$

6. *Transamidation*

Reaction of carboxamides with amines can result in transfer of the acyl group of the amide to the nitrogen of the amine. In such cases the amide acts as the acylating

$$R^1CONR^2R^3 + HNR^4R^5 \longrightarrow R^1CONR^4R^5 + R^2R^3NH \tag{551}$$

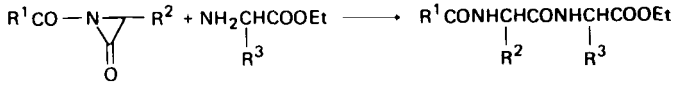
agent. Formylation of aliphatic amines with DMF takes place in the presence of carbon dioxide to afford *N*-alkylformamides[1325]. Cyanoacetamide also participates to transfer a cyanoacetyl group, while acetamide reacts poorly and *N,N*-dimethylacetamide (DMAC) fails to react. Aromatic amines are not acylated by this procedure. The mechanism of transacylation is assumed to involve initial reaction of the amine with carbon dioxide to produce the corresponding carbamic acid, which then reacts with DMF to form the observed product and expel carbon dioxide (equation 552).



(552)

More recently it has been found that aliphatic amines undergo both uncatalysed and acid-catalysed acylations with formamide, DMF and DMAC[1326]. Although aromatic amines again fail to react under these conditions, base-catalysed formylation of aromatic amines can be accomplished with DMF[1318].

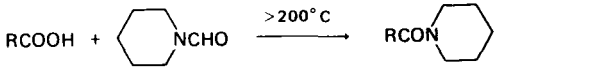
N-acylaziridones react with ethyl esters of amino acids in a novel transamidation process leading to peptides (equation 553)[1327].



(553)

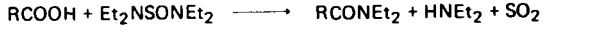
In a somewhat different type of transamidation, acetamide has been reported to react with aliphatic acids at elevated temperatures to give moderate yields of primary amides (equation 554)[1328]. Similarly, *N*-formylpiperidine reacts with fatty acids to afford *N*-acylpiperidides (equation 555)[1329]. Treatment of DMF at

(554)



(555)

reflux with carboxylic acids in the presence of phosphorus pentoxide leads to formation of *N,N*-dimethyl carboxamides[1330]. Reactions of carboxylic acids with bis(diethylamino)sulphoxide in benzene gives rise to *N,N*-diethyl carboxamides (equation 556)[1331].



(556)

B. Amides by Hydrolysis and Cleavage Reactions

1. *Hydrolysis of nitriles*

Hydrolysis of nitriles to amides has long been recognized as a useful synthetic procedure (equation 557). The hydrolysis may be arrested at the intermediate

(557)

amide stage by using concentrated sulphuric acid, basic hydrogen peroxide, polyphosphoric acid or boron trifluoride[1332]. However, since none of these methods has been found to be universally acceptable for aliphatic and unsaturated nitriles in particular, the search for new catalysts and milder reaction conditions has continued.

Several modifications of traditional hydrolytic methods have proved effective for nitrile hydrolysis. The sulphuric acid method of hydrolysis has been conducted in sulphur trioxide while continuously adding just enough water to convert the sulphur trioxide to 100% sulphuric acid. This procedure appears to be generally satisfactory for hydrolysing unsaturated nitriles, such as methacrylonitrile[1333]. Aromatic nitriles are readily converted to the corresponding amides by reaction at 40°C with 30% methanolic hydrogen peroxide containing potassium bicarbonate

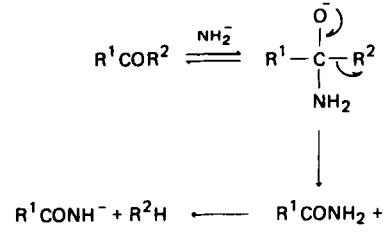
and cyclohexene[1334]. Cyclohexene is converted to cyclohexene oxide during the reaction.

Carboxamides can be prepared by the reaction of nitriles with formic acid and hydrogen chloride or hydrogen bromide[1335]. This efficient method gives excellent yields of amides from aliphatic, aromatic and unsaturated nitriles.

Nitriles are converted to amides under essentially neutral conditions upon refluxing with manganese dioxide in aqueous dioxane[1336]. Palladium chloride-catalysed hydrolysis of nitriles also takes place without added acid or base[1337]. Two other mild methods for effecting hydrolytic production of amides under neutral conditions involve the use of chloropentammineruthenium(III) chloride, $[(NH_3)_5RuCl]Cl_2$[1338] or homogeneous tertiary phosphine–metal–hydroxy complexes such as *trans*-$Rh(OH)(CO)(PPh_3)_2$[1339].

2. *Cleavage of ketones*

Non-enolizable ketones undergo cleavage with sodium amide to form carboxamides and a hydrocarbon residue. This rather general process, known as the Haller–Bauer reaction[1340], occurs by attack of amide ion at the carbonyl carbon, followed by decomposition of the adduct into a hydrocarbon anion and an amide (equation 558). If R^2 is more electron-attracting than R^1 the cleavage will occur in

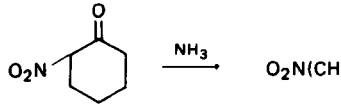


(558)

the manner shown in the accompanying scheme. The Haller–Bauer reaction is one of the few methods which is satisfactory for the synthesis of amides possessing a quaternary α-carbon.

The recent finding that commercial sodium amide can be used for ketone cleavage if it is activated by equimolar amounts of 1,4-diazabicyclo[2.2.2]octane, simplifies the experimental procedure, which had previously required freshly prepared sodium amide[1341].

Reaction of 2-nitrocyclohexanone with ammonia results in Haller–Bauer-type cleavage to form ω-nitrocaproamide in 94% yield (equation 559)[1342].



(559)

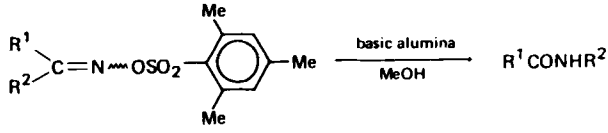
C. Amides by Rearrangements

The Beckmann rearrangement[836-838,1343], involves rearrangement of oximes to substituted amides under the influence of phosphorus pentachloride, concentrated sulphuric acid or various other reagents (equation 560). The group *trans* to the hydroxy group is usually the one which migrates.

(560)

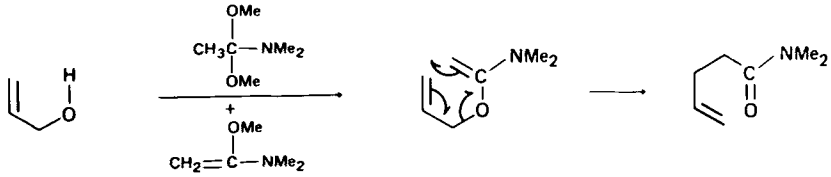
Among the new reagents which have been shown to catalyse Beckmann rearrangements, triphenylphosphine in carbon tetrachloride effects the conversion of various alkanone oximes to amides in good yields under mild, neutral conditions[1344]. Aldoximes are isomerized to unsubstituted amides by means of silica gel in refluxing xylene[1345]. This procedure is claimed to be superior to other known methods of aldoxime rearrangement. Ketoximes have been found to undergo rearrangement in HMPA at 225–240°C to afford the appropriate amides in good yields[1346]. *N,N*-Dimethyldichloromethaniminium chloride effects rearrangement of ketoximes to amides, while aldoximes are converted to nitriles with this reagent[1347].

Reaction of ketones with *O*-mesitylenesulphonylhydroxylamine affords *O*-mesitylenesulphonyloximes, which in turn undergo facile rearrangement to form carboxamides on treatment with basic alumina in methanol (equation 561)[1348].



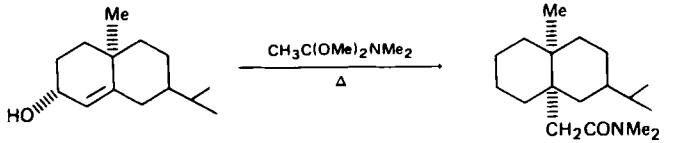
(561)

In 1964, Eschenmoser and coworkers reported a novel Claisen-type rearrangment which results in transformation of allylic alcohols into γ,β-unsaturated amides (equation 562)[1349]. These reactions are accomplished by heating the appropriate

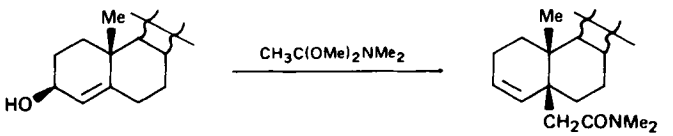


(562)

alcohol with a mixture of *N,N*-dimethylacetamide dimethyl acetal and 1-dimethylamino-1-methoxyethylene in xylene. Formation of the unsaturated amide occurs via a [3,3]-sigmatropic rearrangement of the ketene *N,O*-acetal formed from the allylic alcohol. The overall result is a shift of the alcohol double bond to the site of the original hydroxyl group and transfer of the CH_2CONMe_2 group to the terminal site of the original allylic system. The stereospecific nature of these reactions is illustrated by equations (563) and (564).

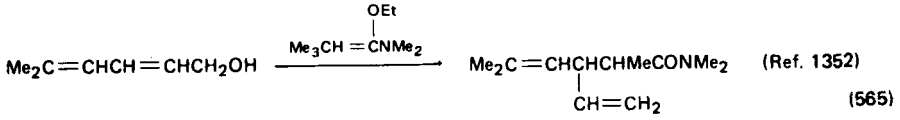


(Ref. 1350) (563)



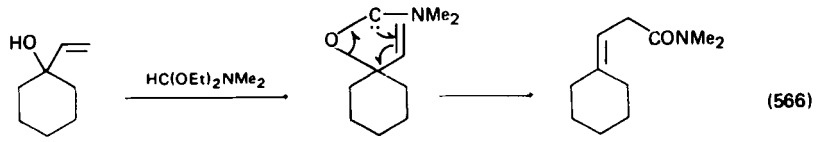
(Ref. 1351) (564)

Reactions of allylic alcohols with 1-dimethylamino-1-methoxypropylene-[1352,1353] and 1-dimethylamino-1-ethoxypropylene[1354] lead to introduction of an α-substituted *N,N*-dimethylpropionamide residue at the terminus of the allylic system (equation 565). Recently, it has been found that allylic alcohols can be



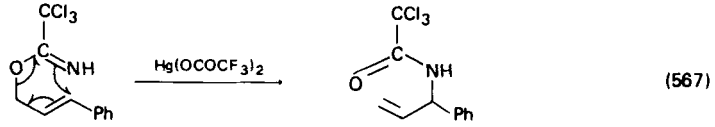
(Ref. 1352) (565)

transformed into homologous amides by *N,N*-dimethylformamide acetals (equation 566)[1355]. These reactions, which lead to transfer of a one-carbon amide residue,



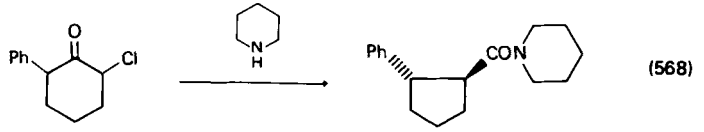
(566)

are assumed to proceed via [2,3]-sigmatropic rearrangement of an intermediate carbene. Allylic trichloroacetimidates, which are conveniently prepared from allylic alcohols and trichloroacetonitrile, undergo both thermal and mercuric ion-catalysed [3,3]-sigmatropic rearrangements to form *N*-allyl trichloroacetamides (equation 567)[1356]. Here, nitrogen, rather than carbon, is transferred to the terminal allylic position.



(567)

The Favorskii rearrangement[871-873] can serve as a method of amide synthesis in the case of certain α-halo-α'-aryl ketones (equation 568)[1357].



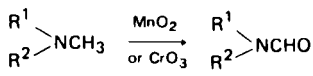
(568)

The Willgerodt reaction, which may be considered as a rearrangement process leading to carboxamides, has been reviewed recently[1358].

The Chapman rearrangement, involving thermal isomerization of *N*-aryl and *N*-alkyl imidates to *N,N*-disubstituted amides, has been discussed in detail elsewhere[1359].

D. Amides by Oxidation

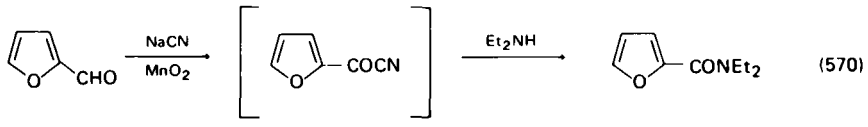
N,N-Dialkylformamides are produced upon treatment of *N*-methyl tertiary amines with oxidizing agents such as manganese dioxide[1360] or chromic anhydride (equation 569)[1361]. Similar oxidations have been accomplished with molecular oxygen in the presence of a platinum catalyst[1362]. Interestingly, *N*-demethylation



(569)

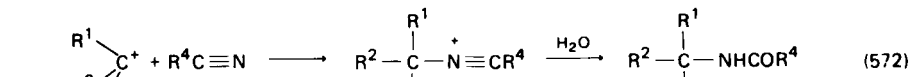
rather than oxidation occurs when platinum-catalysed aerations are carried out in aqueous solutions[1363].

Oxidation of aromatic and α,β-unsaturated aldehydes with manganese dioxide in the presence of sodium cyanide and ammonia or an amine leads to amides (equation 570)[1364]. The mechanism of this reaction appears to involve intermediate formation of an acyl cyanide.



(570)

Treatment of 1-acylsemicarbazides with oxygen produces amides in moderate to good yields (equation 571)[1365]. The reaction is assumed to proceed through a diacyldiazene intermediate, which loses carbon monoxide and nitrogen.



(571)

E. Amides by Acylamination

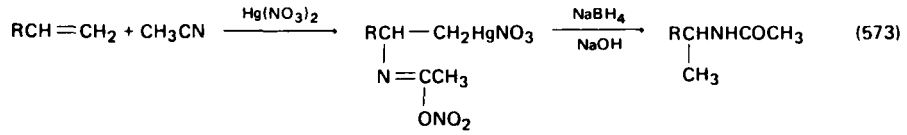
Reactions in which an acylamino (–NHCOR) function is introduced directly into an appropriate substrate are classified as acylaminations.

The Ritter reaction[1366] constitutes the most versatile method for the synthesis of amides by acylamination (equation 572). This reaction involves addition of a

(572)

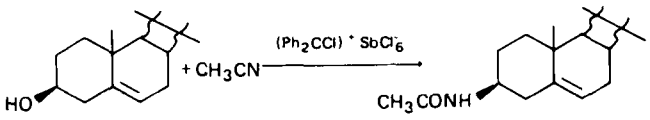
nitrile to a carbonium ion in the presence of sulphuric acid to form a nitrilium salt. Subsequent dilution of the reaction mixture with water affords an *N*-substituted amide.

A number of recent applications of the Ritter reaction have involved new methods for the generation of carbonium ions necessary for combination with the nitrile component of the reaction. With olefinic substrates, hydrogen fluoride is claimed to be superior to sulphuric acid[1367]. Treatment of cyclic or terminal olefins with mercury(II) nitrate in acetonitrile and subsequent reduction of the intermediate organomercury compounds with sodium borohydride provides a convenient method for acylamination of olefins (equation 573)[1368].



(573)

Although the Ritter reaction works with benzylic alcohols[1369], primary aliphatic carbinols do not react satisfactorily. This limitation can be circumvented by treatment of primary alcohols such as *n*-decanol with the hexachloroantimonate salts of chlorodiphenylmethylium, dichlorophenylmethylium or pentachloroallylium cations in nitrile solvents[1370]. These cationic reagents can also be employed to convert cholesterol to 3-β-acetamidocholest-5-ene (equation 574), a transformation that does not proceed under simple Ritter conditions.



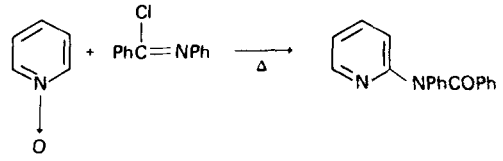
(574)

Cyanohydrins participate in the Ritter reaction with *t*-butyl alcohol to afford *N*-*t*-butyl α-hydroxy amides (equation 575)[1371]. Oxidation of the α-hydroxy

$$RCH(OH)CN \xrightarrow[H_2SO_4]{t\text{-}BuOH} RCH(OH)CONHBu\text{-}t \xrightarrow[2.\ H_3O^+]{1.\ CrO_3} RCOCOOH \qquad (575)$$

amides followed by acid hydrolysis leads to α-keto acids. Anodic oxidations of alkyl iodides[1372] and alkanoic esters[1373] in the acetonitrile solution produce *N*-substituted acetamides. These reactions appear to take place through a carbonium-ion mechanism analogous to the Ritter reaction. Tertiary alkyl bromides react with nitriles to form amides in a modification of the Ritter reaction which does not require an internal catalyst[1374].

Direct acylamination of pyrindine *N*-oxides with an imidoyl chloride can be carried out by heating the reactants in ethylene chloride (equation 576)[1375].



(576)

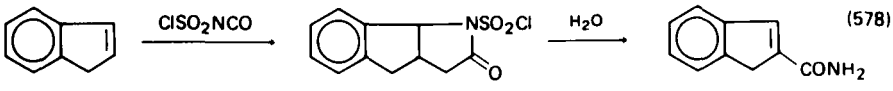
F. Amides by Carboxamidation

A number of methods for electrophilic aromatic carboxamidations have been reviewed[1376,1377]. Recently, direct carboxamidation of aromatic substrates has been achieved in modest yields with urea in the presence of excess aluminium chloride (equation 577)[1377]. 2-Indenecarboxamide has been synthesized in good

$$ArH + H_2NCONH_2 \xrightarrow{AlCl_3} ArCONH_2 \qquad (577)$$

yield by hydrolysis of the intermediate lactam formed by treatment of indene with chlorosulphonyl isocyanate (equation 578)[1378]. This procedure represents a potentially general method for carboxamidation of unsaturated substrates.

α,β-Acetylenic carboxamides can be conveniently prepared by reacting α-trimethylsilylalkynes with aminocarbonyl chlorides in the presence of a molar equivalent of aluminium chloride (equation 579)[1379].



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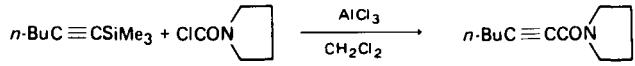
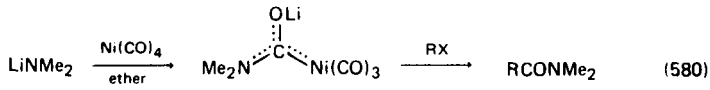


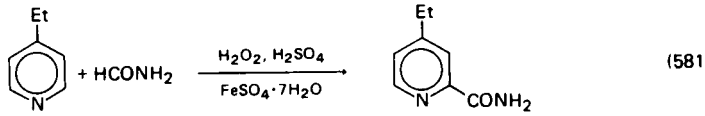
(579)

Nucleophilic carboxamidation of alkyl, aryl, vinyl and acyl halides can be accomplished in good yields with lithium dimethylcarbamoylnickel tricarbonylate, which is prepared from lithium dimethylamide and nickel tetracarbonyl in ether (equation 580)[1380].



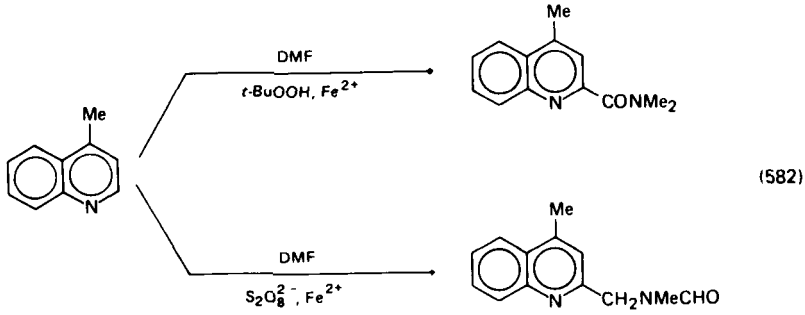
(580)

Free-radical carboxamidation of heteroaromatic bases has been accomplished by reaction of the carbamoyl (•$CONH_2$) radical, formed by hydrogen abstraction from formamide, with the protonated form of various heteroaromatics including pyridine, quinoline, isoquinoline, pyrazine, quinoxaline, benzothiazole and benzimidazole (e.g. equation 581)[1381,1382]. Substitution takes place selectively at the most



(581)

electrophilic positions of the heterocyclic substrate. When DMF is allowed to react with quinoline in the presence of certain oxidizing agents, the reaction is complicated by formation of two radicals from the DMF molecule. However this difficulty can be overcome by varying the nature of the oxidant[1382,1383]. For example, lepidine yields mainly the 2-carboxamide upon treatment with DMF in the presence of *t*-butylhydroperoxide and ferrous ion, while substitution at a methyl group of DMF occurs when peroxidisulphate is employed as the oxidizing reagent (equation 582).



(582)

Photochemical reactions of formamide with benzene and alkylbenzenes in the presence of acetone, benzophenone or acetophenone as photoinitiators lead to

carboxamidation of the ring and side chains, respectively[1384]. Thus, benzene gives benzamide and toluene is converted mainly to phenylacetamide along with some *o*-toluamide. This method suffers from the disadvantage that yields rarely exceed 30%.

Halogenation or oxidation of the alkyl or acyl complexes derived from sodium tetracarbonylferrate(−II)[257] in the presence of amines affords amides via a process which may be regarded as carboxamidation of alkyl halides or tosylates (equation 583). Aryl, heterocyclic and vinylic halides undergo carboxamidation upon reaction

$$n\text{-}C_5H_{11}Br \xrightarrow[2.\ I_2,\ Et_2NH]{1.\ Na_2Fe(CO)_4,\ CO} n\text{-}C_5H_{11}CONEt_2 \qquad (583)$$

with carbon monoxide and primary and secondary amines in the presence of a dihalobistriphenylphosphinepalladium(II) catalyst[1385]. The stereospecificity of this reaction is demonstrated in equation (584).

$$\begin{matrix} H \\ Ph \end{matrix}\!\!>\!C=C\!<\!\!\begin{matrix} Br \\ H \end{matrix} + CO + PhNH_2 \xrightarrow[60^\circ C,\ 1\ atm]{PdBr_2Ph_3} \begin{matrix} H \\ Ph \end{matrix}\!\!>\!C=C\!<\!\!\begin{matrix} CONHPh \\ H \end{matrix} \qquad (584)$$

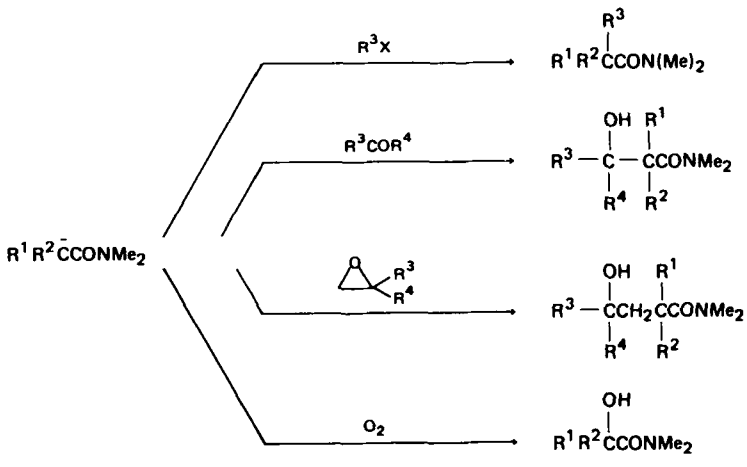
Related carboxamidations have been performed on alkyl and vinyl halides using nickel tetracarbonyl and secondary amines in the presence of alkoxide bases[252,253].

G. Amides by Condensation Reactions

Several new procedures for amide synthesis involve condensations of electrophilic reagents with α-carbanions derived from amides. These reactions, which bear a strong resemblance to active hydrogen condensations involving esters, can be used for the synthesis of various elaborated amides from readily available precursors.

Generation of α-carbanions from *N,N*-dialkylcarboxamides can be effected by means of sodium amide[1386-1389], *n*-butyllithium[1390] or LDA (equation 585)[1391,1392]. The resulting α-anions react with alkyl

$$R^1\text{—}\underset{R^2}{\underset{|}{C}}HCONMe_2 \xrightarrow{B^-} R^1\text{—}\underset{R^2}{\underset{|}{C}}CONMe_2^- \qquad (585)$$



(586)

halides[1386-1388,1390,1391], aldehydes and ketones[1390], epoxides[1389] and molecular oxygen[1392] to afford α-alkyl, β-hydroxy, γ-hydroxy and α-hydroxy amides, respectively (equation 586).

Zinc derivatives analogous to Reformatsky reagents can be prepared from α-bromo-*N*,*N*-dialkylamides[1393].

Reaction of *N*-alkylacetamides with two equivalents of *n*-butyllithium produces 1,3-dianions, which react with aryl aldehydes to produce *N*-alkyl-β-hydroxy amides[1394].

$$CH_3CONHR^1 \xrightarrow{2\,n\text{-BuLi}} \bar{C}H_2CO\bar{N}R^1 \xrightarrow{R^2CHO} R^2CH(OH)CH_2CONHR^1 \quad (587)$$

Reactions of aldehydes and ketones with DMF in THF–ether in the presence of LDA at −78°C produces α-hydroxy-*N*,*N*-dimethylamides (equation 588)[1395].

$$\begin{matrix} R^1 \\ R^2 \end{matrix}\!\!>\!C{=}O + HCONMe_2 \xrightarrow{LDA} R^1{-}\overset{OH}{\overset{|}{C}}CONMe_2 \quad (588)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad R^2$$

Metalated *N*-phenyl phenylketenimines react with benzaldehyde or α,β-unsaturated aldehydes in a Wittig-type process to yield α-phenylacrylanilides (equation 589)[1396].

$$RCHO + Ph{-}\overset{M^+}{\overset{|}{\bar{C}}}{=}C{=}NPh \longrightarrow PhC{=}\overset{M^+}{\overset{|}{C}}{-}\bar{N}Ph$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad R{-}CH{-}O$$
$$\xrightarrow{H_3O^+} RCH{=}C(Ph){-}\overset{O}{\overset{\|}{C}}{-}NHPh \quad (589)$$

Metalation of α,β-ynamines by alkylithium–TMEDA complexes leads to formation of lithium derivatives which undergo terminal alkylation on treatment with alkyl halides. Subsequent hydrolysis or alcoholysis of the elaborated ynamines affords amides or esters, respectively (equation 590)[1397].

$$CH_3C{\equiv}C{-}N \xrightarrow[TMEDA]{t\text{-BuLi}} LiCH_2C{\equiv}C{-}N \xrightarrow{RX}$$

$$RCH_2C{\equiv}C{-}N \xrightarrow[Et_2O]{alumina} RCH_2CH_2CON \quad (590)$$

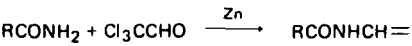
H. Amides by Miscellaneous Methods

Formamides can be prepared by carbonylation of primary[1398] and secondary amines[1399,1400] using ruthenium[1398,1400] and copper[1399] catalysts (equation

591). Formylation of secondary amines has also been accomplished by reaction with carbon dioxide and hydrogen[1401], and by treatment of the amine with chloroform and aqueous sodium hydroxide in the presence of a phase-transfer catalyst such as triethylbenzylammonium chloride[1402]. The latter reaction involves attack of dichlorocarbene at the amine nitrogen.

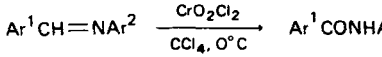
(591)

N,β,β-Dichlorovinylamides have been prepared recently by reaction of chloral with amides in the presence of powdered zinc (equation 592)[1403].



(592)

Treatment of *N*-phenylimines with chromyl chloride affords anilides in good yields (equation 593)[1404]. The reaction presumably involves formation of intermediate oxaziranes, which isomerize to the observed amides.



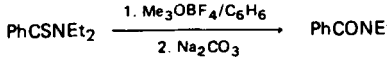
(593)

Reductive hydrolysis of azlactones in alcoholic ammonia at room temperature leads to α-benzoylamino acid amides (equation 594)[1405]. This procedure is more

(594)

convenient than earlier methods which require hydrolysis of the azlactone to the unsaturated acylamino acid followed by a hydrogenation step.

A general method for conversion of *N*,*N*-dialkylthioamides to *N*,*N*-dialkylcarboxamides involved treatment of the thioamide with trimethyloxonium fluoroborate in dry benzene, and then hydrolysis with aqueous sodium carbonate (equation 595)[1406].



(595)

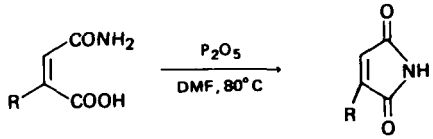
VII. SYNTHESIS OF IMIDES

Several recent reviews provide detailed coverage of general methods for the synthesis of imides[1407-1409]. In light of this, we have chosen to outline several procedures which have appeared since these articles were written.

A. Imides by Acylation Reactions

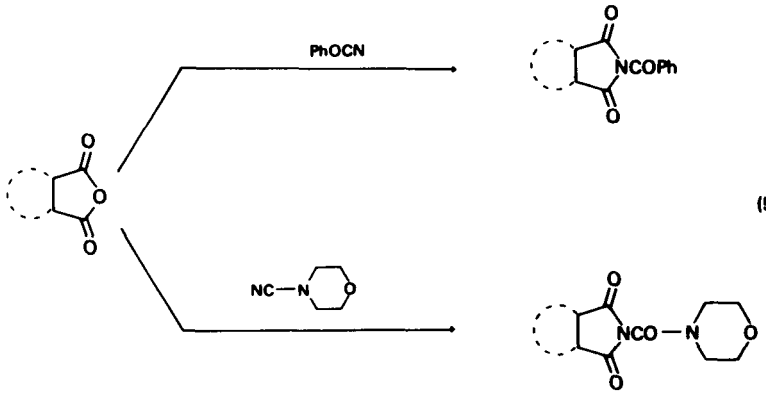
Acylations of amines and amides with acyl halides or anhydrides constitute a general method for the preparation of imides. For example, the synthesis of various

cyclic imides can be accomplished by treatment of cyclic anhydrides with ammonia or an amine to form an amic acid, which is then cyclized thermally or in the presence of a suitable dehydrating agent. In connection with the synthesis of the *C*-nucleoside, showdomycin, phosphorus pentoxide suspended in DMF has been demonstrated to be a mild and potentially general reagent for cyclization of α-substituted maleamic acids where other procedures fail (equation 596)[1410].



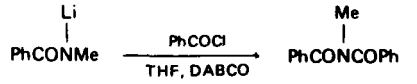
(596)

Cyclic anhydrides of aromatic and cycloaliphatic dicarboxylic acids react with cyanates and cyanamides to form *N*-acylated imides (equation 597)[1411].



(597)

Acylation of mono- and di-*N*-lithio salts of amides has been accomplished with aroyl chlorides in the presence of Lewis bases such as 1,4-diazabicyclo-[2.2.2]octane (DABCO) (equation 598). In the absence of DABCO, which in-



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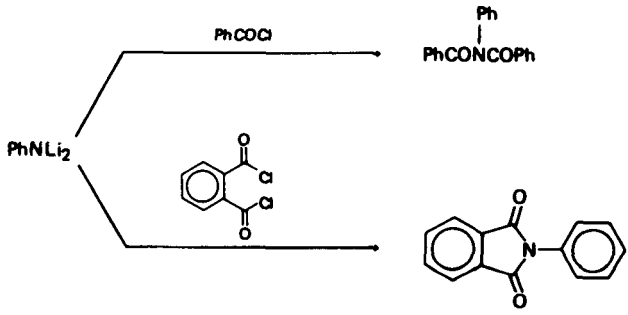


(599)

creases the rate of acylation through coordination with the lithium cation, yields of imides drop sharply[1412]. The *N,N*-dilithio salts of aniline and benzamide react with aroyl chlorides in the presence of DABCO to form dibenzamides and tribenzamides, respectively (equations 599 and 600). Dilithioaniline also condenses with phthaloyl

$$PhCONLi_2 \xrightarrow{PhCOCl} (PhCO)_3N \qquad (600)$$

chloride to produce *N*-phenylphthalimide. These acylation procedures offer considerable promise as a general approach to imide synthesis, with the possible limitation that aliphatic acyl halides may be unsatisfactory because of the strongly basic character of the lithio salts employed. Acylation of primary amides with aliphatic chlorides in methylene chloride in the presence of pyridine, 2-methylpyridine or 2,6-dimethylpyridine leads directly to triacylamides rather than simple imides (equation 601)[1413].

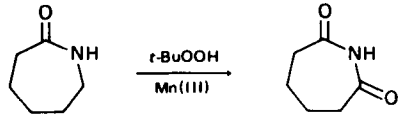
$$2\ RCOCl + RCONH_2 \xrightarrow[-20\ to\ 40^\circ C]{CH_2Cl_2} (RCO)_3N \qquad (601)$$

Reaction of cyclic imino esters with acyl chloride produces *N*-acyllactams (equation 602)[1414]. This procedure would appear to be applicable to acyclic imino esters also.

(602)

B. Imides by Oxidation Reactions

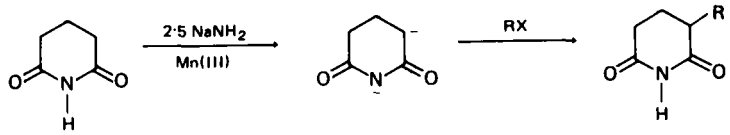
Oxidation of lactams and *N*-alkylamides to imides has now been developed into a useful synthetic method[1415]. Excellent results are obtained with lactams by using a hydroperoxide or peroxy acid in the presence of manganese(II) or manganese(III) acetylacetonates. This mild oxidative procedure represents the first convenient method for synthesizing several relatively inaccessible imides such as adipimide. Acylic *N*-alkylamides are oxidized to linear imides more satisfactorily with peroxyacetic acid than with hydroperoxide oxidants.



(603)

C. Imides by C- and N-Alkylations

Elaboration of preformed imides can be effected by abstraction of the NH proton as well as an α-hydrogen to form a dianion intermediate such as that derived from glutarimide[1416]. Subsequent alkylation of the dianion occurs exclusively at the more nucleophilic carbanion site to produce 2-alkyl glutarimides (equation 604). Aldehydes and ketones react with the glutarimide dianion to afford 2-(α-hydroxy)alkylglutarimides, while reactions with aromatic esters produce 2-aroylglutarimides. Similar dianion approaches have been used to prepare substituted

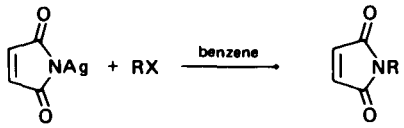


(604)

2,4-morpholinediones[1416], 2,4-thiomorpholinediones[1416] and 2,4-thiazolidinediones[1417]. Phenylacetylureas can be converted to trianions, which undergo regiospecific alkylations at the benzylic position (equation 605)[1418].

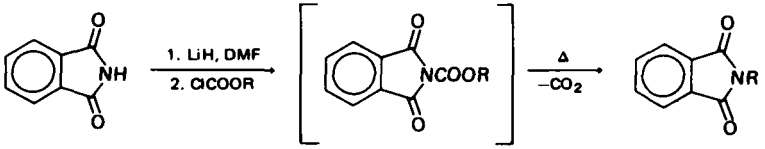
$$PhCH_2CONHCONHR^1 \xrightarrow[NH_3]{4\cdot5\ KNH_2} Ph\bar{C}HCO\bar{N}CO\bar{N}R^1 \xrightarrow{R^2X} PhCHR^2CONHCONHR^1 \qquad (605)$$

Preparation of *N*-alkylimides can often be realized by one or more of the classical acylation reactions described above. However, certain *N*-alkylamic acids are cyclized with difficulty, and *N*-alkylation of the unsubstituted cyclic imide becomes the preferred method of synthesis. Preparation of *N*-alkylmaleimides, which are often available in low yields by cyclization of *N*-alkylmaleamic acids, is smoothly effected by coupling of alkyl or aralkyl halides with the silver salt of maleimide (equation 606)[1419]. Another convenient procedure for *N*-alkylation of



(606)

imides consists of initial conversion of the imide to the lithio salt by means of lithium hydride in DMF, followed by addition of a chloroformate ester to the reaction mixture at 60–100°C[1420]. The intermediate *N*-carboethoxyimide undergoes decarboxylation at this temperature to afford the desired *N*-alkylimide (equation 607).



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VIII. ACKNOWLEDGMENTS

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Synthesis of carboxylic acids, esters and their derivatives
Edited by Saul Patai and Zvi Rappoport

CHAPTER **2**

Appendix to 'The synthesis of carboxylic acids and esters and their derivatives'†

†The material in this Appendix is divided in the same manner as in the original Chapter 7 in Supplement B. Corresponding section numbers in this Appendix are preceded by an asterisk. Note that some section numbers are omitted while some new ones (not preceded by an asterisk) have been added. Structures, equations, tables, schemes and references run continuously in the original chapter and the Appendix.

*I. INTRODUCTION

This Appendix on the synthesis of carboxylic acids and esters and their derivatives covers the primary literature from 1975 through mid-1987. Recent references have been included for all approaches to the synthesis of these compounds, including references to the general preparative methods presented in the original chapter.

The Appendix organization follows identically that used in the original chapter, and the reader will find information on the same topic by successively reading the original section of the chapter and then referring to the same numbered main section in this Appendix. In instances where little or no new information has been published regarding a specific synthetic approach discussed in the original chapter, the corresponding subsection has been eliminated in the Appendix. Conversely, new synthetic approaches not covered in the

original chapter have been added to the appropriate sections of this Appendix under final subsections entitled 'Miscellaneous···'.

Structures, equations, tables, schemes and references are numbered in continuation of those in the original chapter.

*II. SYNTHESIS OF CARBOXYLIC ACIDS

A large number of review articles have been published dealing with the preparation of carboxylic acids. These review articles have included descriptions of the general synthetic methods used to prepare carboxylic acids[1421-1429], while more specific reviews dealing with the preparation of aliphatic carboxylic acids[1430,1431], the production and uses of aliphatic carboxylic acids containing fluorine[1432], the production prospects of benzenecarboxylic acid from coal and related substances[1433], phenolic carboxylic acids[1434], the preparation of C^{14}-labeled carboxylic acids[1435], stereoselective synthesis of β-hydroxycarboxylic acids[1436], the synthesis and uses of β-keto acids[1437], the preparation and properties of chromancarboxylic acids[1438], the isolation of monomeric carboxylic acids from the stereospecific reactions and interactions in tri-*ortho*-thymotide clathrates[1439], the use of oxazolines for the synthesis of carboxylic acids[1440], recent developments in the production of citric, lactic, propionic and ascorbic acids[1441], the synthesis of antiinflammatory α-arylalkanoic acids by a 1,2-aryl shift[1442], the synthesis of L-2-oxothiazolidine-4-carboxylic acid using phenyl chloroformate[1443], the preparation and properties of 3d transition metal trinuclear carboxylate complexes[1444] and the synthesis and stereochemistry of β-hydroxyacids via aldol-type condensations[1445] have also appeared. In addition, review articles describing the preparation of heteroatom-containing carboxylic acids have been published which include the synthesis of phosphorus-containing carboxylic acids[1446], the synthesis of monothio[1447] and dithio carboxylic acids[1448], and the synthesis of selenium and tellurium isologs of carboxylic acid derivatives[1449]. In the case of nitrogen-containing carboxylic acids, published reviews include a survey of N-functional carboxylic acid and thiocarboxylic acid derivatives[1450], the preparation of pyridine carboxylic acids[1451,1452], a synthetic study of α-amino acids and related compounds using isonitriles[1453], a review of other carboxylic acids with substituents containing nitrogen atoms[1454] and a review of the rearrangements of penicillanic acid derivatives[1455].

Preparation of carboxylic acids by oxidative methods has been discussed in several reviews including the preparation of monocarboxylic acids by the oxidation of hydrocarbons using oxygen[1456,1457] and ozone[1458], and the preparation of dihydroxy and trihydroxy carboxylic acids via the oxidation of trihydric alcohols[1459].

The use of coupling reactions to synthesize carboxylic acids from lower carbonyl compounds[1460], and via solvolysis[1461], and the Kolbe electrolysis[1462] have also appeared in addition to several reviews dealing with the synthesis of carboxylic acids by carbonylation[1463-1468].

Recent reports have indicated an increase in the use of biochemical approaches to the synthesis of various organic molecules, including carboxylic acids. Thus, reviews on the production of organic acids by the fermentation of hydrocarbons[1469], by using yeasts and the mechanism of this fermentative conversion[1470], and by using mycelial fungi[1471], fungal cultures[1472] and immobilized microbial cells[1473], as well as reviews on the fermentative production of specific acids such as citric[1474-1476], itaconic[1474], lactic[1474], gluconic[1474], fumaric[1476], glycolic[1476], optically active α-hydroxy[1477,1478], β-hydroxy[1479] and amino acids[1478-1481] have been published.

Dicarboxylic and polycarboxylic acid preparation has also been reviewed in numerous publications which have included the synthesis of aliphatic dicarboxylic acids[1482-1484], dicarboxylic acid derivatives from fatty acids[1485], aromatic dibasic acids containing an

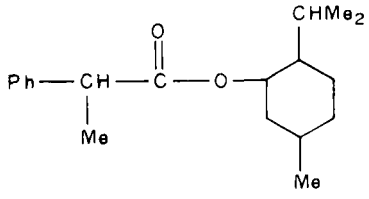
azo bond via electrochemical synthesis[1486], dicarboxylic acids from alkanes using microorganisms[1487–1489], polycyclic dicarboxylic acid derivatives useful as flame-retardant monomers prepared from chlorinated petroleum hydrocarbons[1490], benzene-polycarboxylic acids from coals[1491], new derivatives of aromatic polycarboxylic acids for use in polymer production[1492], polymers produced from diaminodicarboxylic acids and their uses[1493] and metal-coordination polymers produced from dicarboxylic acids and divalent metals[1494].

Several interesting review articles report the use of aliphatic carboxy acids and their derivatives as pesticides[1495], the chemical degradation and mode of action of chlorinated aliphatic acid herbicides[1496], the mechanism of reactions of carboxylic acids and their derivatives[1497] and the photochemical reactions of carboxylic acids and their derivatives[1498].

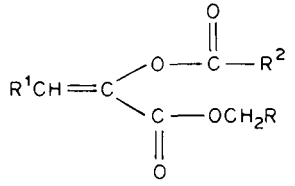
*A. Acids by Hydrolysis Reactions

*1. Hydrolysis of esters

Acid hydrolysis of the 1-menthol ester of 2-phenylproprienic acid (equation 608) has been reported[1499] to produce a 78% yield of (*R*) 2-phenylproprienic acid in a 69:31 enantiomeric ratio, while similar yields of α-keto acids have been obtained[1500] by acid hydrolysis of unsaturated glycolic esters (equation 609).



$$\xrightarrow[12\ h]{HCl,\ 50\ ^{\circ}C} PhCH(Me)COOH \qquad (608)$$



$$\xrightarrow{H_3O^+} R^1CH_2COCOOH \qquad (609)$$

$R^1 = C_6 - C_8(n\text{-alkyl})$

$R^2 = Et, n\text{-}Pr$

Conversion of acids into *t*-butyl esters is the method of choice for protecting acids since these esters are stable under neutral and basic conditions, but are readily hydrolyzed under acidic conditions. Hydrolysis of *t*-butyl esters may be accomplished in anhydrous acid[1501,1502], by reaction at room temperature with excess trifluoroacetic acid[1503,1504] (equation 610), using hydrochloric acid in dichloromethane at room temperature[1505] or

$$PhRC(OH)CH_2CH{=}CHCOOBu\text{-}t + CF_3COOH \xrightarrow[4\,h]{25\ ^{\circ}C} PhRC(OH)CH_2CH{=}CHCOOH \qquad (610)$$

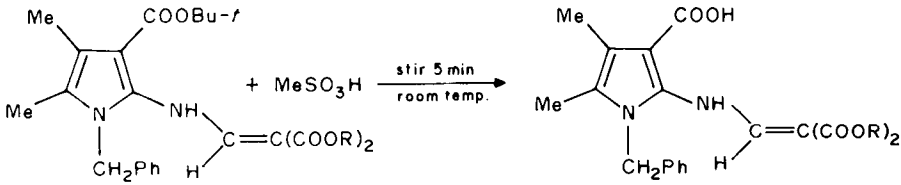
R = Ph, Me, cyclohexyl

by reaction in refluxing dioxane–sulfuric acid mixtures[1506]. If a two-phase reaction medium consisting of aqueous mineral acids in the presence of lipophilic quaternary onium salt such as hexadecyltributylphosphonium bromide at room temperature is used[1507], a highly selective *t*-butyl ester cleavage occurs (equation 611) which does not effect alcohol, ether, alkene, nitrile, carboxylic amide or carboxylic esters of primary alcohol functions which may be present in the molecule. While esters of primary alcohols can also be hydrolyzed using this approach, more drastic conditions are required[1507].

$$\text{RCOOBu-}t + C_{16}H_{34}(n\text{-}C_4H_9)_3\overset{+}{P}Br \xrightarrow[\text{room temp.}]{HX} \text{RCOOH} \qquad (611)$$

R = alkyl, aryl; X = HSO_4, Br, Cl

Other reagents which have been used successfully in the selective hydrolysis of *t*-butyl esters are *p*-toluene[1508] and methane[1509] sulfonic acids. Reaction of the dimethyl or diethyl ester of *N*-[1-benzyl-3-*t*-butoxycarbonyl-4,5-dimethylpyrrol-2-yl]aminomethylenemalonate with methanesulfonic acid affords diester products where only the *t*-butyl ester function in the triester starting material has reacted (equation 612).



(612)

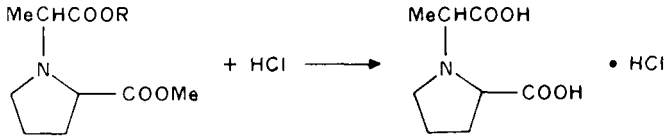
Acid hydrolyses of nitrogen-containing esters have also been reported to proceed readily as in the reaction of *N*-alkyl-*N*-hydroxy-α-aminocarboxylic acid ethyl esters with aqueous hydrochloric acid[1510] (equation 613) to produce the hydrochloride salt of *N*-alkyl-*N*-hydroxy-α-aminocarboxylic acids. If this reaction is attempted using anhydrous

$$\text{RN(OH)CH}_2\text{COOEt} + \text{HCl} \xrightarrow[\text{reflux 30 min}]{H_2O} \text{R}\overset{+}{\text{N}}\text{H(OH)CH}_2\text{COOH}\ Cl^- \qquad (613)$$

R = *i*-Pr, *t*-Bu

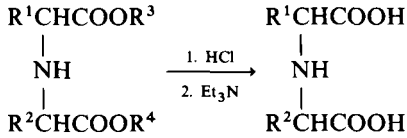
hydrogen chloride, the hydrochloride salt of the starting ester is the only product isolated and no cleavage of the ester is observed. Similar results have been reported[1511] during the acid-catalyzed hydrolysis of a,α′-iminodicarboxylates, with the added observation that the configuration present in the starting material is retained in the α,α′-iminodicarboxylic acids produced (equations 614 and 615). Comparison[1511] of the acid-catalyzed hydrolysis of several N^6-[(1-ethoxycarbonyl)ethyl] lysine methyl esters with the alkali ion exchange hydrolysis of the same molecules produced the results shown in equation 616. Acid-catalyzed hydrolysis of ethyl *N*-(4,4-diphenylbut-3-enyl)-3-piperidinecarboxylate (equation 617) is reported[1512] to produce the corresponding free carboxylic acid.

The use of Lewis acids, in the form of aluminum halides, alone[1513] or coupled with a thiol[1514] (equation 618) has been reported to dealkylate esters to produce acids in good to excellent yields (Table 43) depending upon the substrate structure. Using the same dealkylating system with lactone starting materials produces[1514,1515] thioacids according to the mechanism shown in equation 619. With γ-butyrolactones and ethanethiol excellent yields of substituted ethylthiobutyric acids have been obtained[1514,1515] (Table 44). Similar



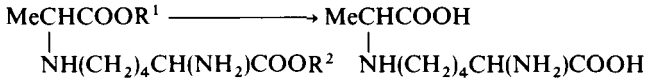
(614)

R	Stereochemistry ester and acid	Yield(%)
Et	2*S*, 1′*R*	87
Et	2*R*, 1′*R*	86
Me_2CHCH_2	2*S*, 1′*S*	89
Me_2CHCH_2	2*R*, 1′*S*	94



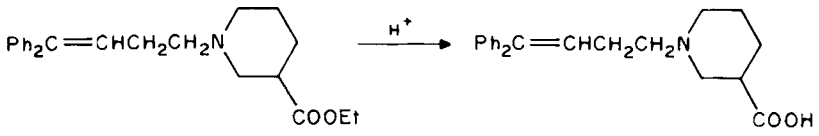
(615)

R^1	R^2	R^3	R^4	Configuration ester and acid	Yield (%)
Me	Me	Et	Et	2*R*, 2′*R*	87
Me	Me	Et	Et	2*S*, 2′*S*	89
Me	Me	Et	Et	(2*R*, 2′*S*)*meso*	86
Me	$PhCH_2$	Me	Et	2*S*, 1′*R*	91
Me	$PhCH_2$	Me	Et	2*R*, 1′*R*	93
Me	$PhCH_2$	Me	Et	2*R*, 1′*S*	86
Me	$PhCH_2$	Me	Me_2CHCH_2	2*S*, 1′*S*	86
$PhCH_2$	$PhCH_2$	Me	Me	2*R*, 2′*R*	87
$PhCH_2$	$PhCH_2$	Me	Me	(2*R*, 2′*S*)*meso*	89



(616)

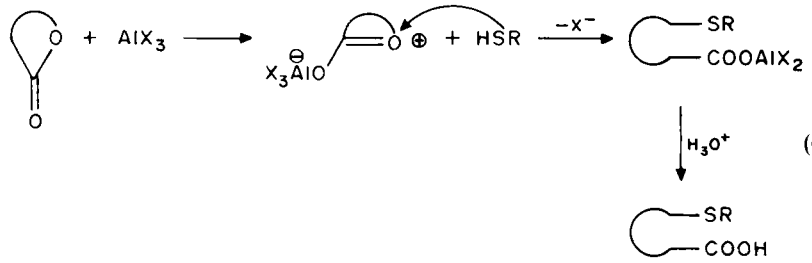
R^1	R^2	Configuration ester and acid	Hydrolysis method	Yield(%)
Et	Me	2*S*, 1′*R*	Acid	83
Et	Me	2*S*, 1′*R*	Alkali	94
Et	Me	2*R*/*S*, 1′*R*	Alkali	90.5
Et	Me	2*S*, 1′*R*/*S*	Acid	84
Et	Me	2*S*, 1′*R*/*S*	Alkali	91



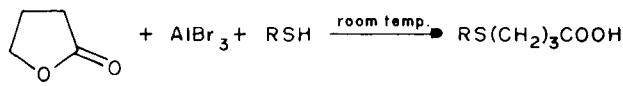
(617)

$$RCOOR^1 + AlX_3 + R^2SH \xrightarrow[\text{stir}]{\text{room temp.}} RCOOAlX_2 + R^1SR^2 + HX \quad (618)$$

$$RCOOAlX_2 \xrightarrow{H_3O^+} RCOOH$$



(619)



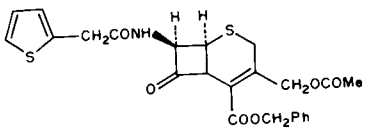
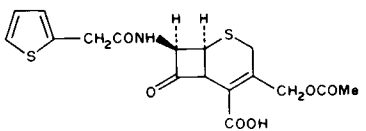
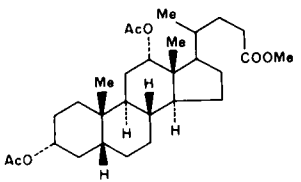
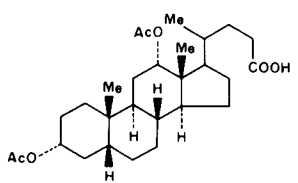
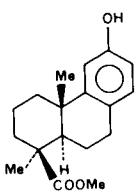
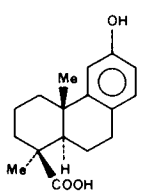
(620)

R	Rx time (h)	Yield(%)
Et	1.3	94.5
n-Pr	1	92
i-Pr	1.2	93.4
i-Bu	3	83

results[1515] have been obtained by reaction of γ-butyrolactone and various alkanethiols (equation 620), and with various lactones and ethane- and benzenethiol (Table 45).

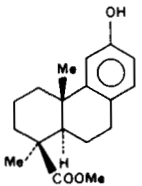
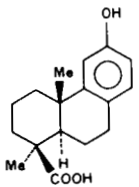
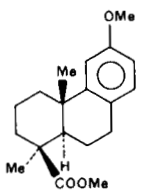
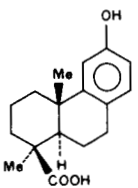
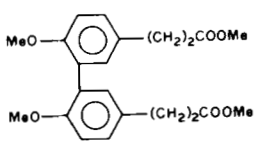
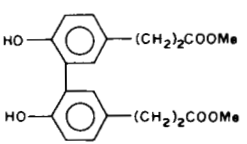
The structure of the molecule to be hydrolyzed as well as the product desired from the hydrolysis are two important criteria to consider when choosing whether to use an acidic or alkali catalyzed reaction. This was demonstrated by the hydrolysis[1516] of (*Z* or *E*)-7-oxo-5-phenyl-6-oxa-4-azaspiro[2.4]hept-4-enes, which upon basic hydrolysis were expected to give 1-amino-2-aryl(methyl)cyclopropanecarboxylic acids, but instead gave only 1-benzoylamino-2-aryl(methyl)cyclopropenecarboxylic acids (equation 621) which resisted further treatment with base. Acid hydrolysis of the spiroheptenes (equation 621) also

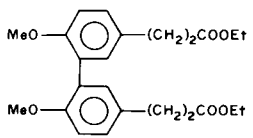
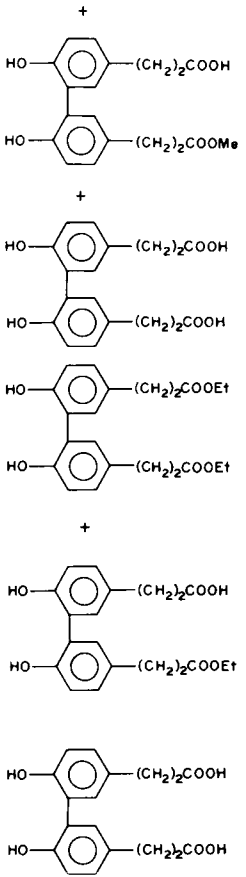
TABLE 43. Lewis acid catalyzed hydrolysis of esters

Substrate	Lewis Acid	Rx time (h)	Product	Yield(%)	Reference
PhCOOMe	$AlBr_3$[a]	6.5	PhCOOH	94	1514
$PhCH_2COOCH_2Ph$	$AlCl_3$[b]	—	$PhCH_2COOH$	87	1513
$PhCOOCH_2Ph$	$AlCl_3$[a]	1.7	PhCOOH	91	1514
$Me(CH_2)_{10}COOCH_2Ph$	$AlCl_3$[a]	1.5	$Me(CH_2)_{10}COOH$	98	1514
	$AlCl_3$[b]	—		57	1513
	$AlBr_3$[a]	9		89	1514
	$AlCl_3$[a]	< 20		98	1514

(continued)

TABLE 43 (*continued*)

Substrate	Lewis Acid	Rx time (h)	Product	Yield(%)	Reference
	$AlBr_3$[a]	5.5		98	1514
	$AlBr_3$[a]	7.5		96	1514
	$AlBr_3$[a,c]	24		18	1514

	$AlBr_3$[a]	50		44 30 30 54 7	1514

[a]Solvent used, ethanethiol.
[b]Solvent used, dichloromethane.
[c]Solvent used, ethanethiol plus dichloromethane.

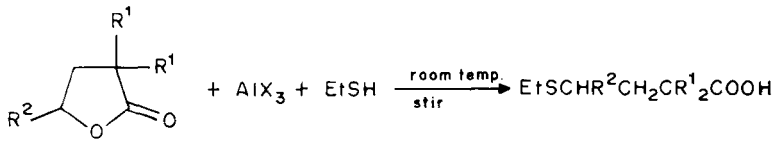
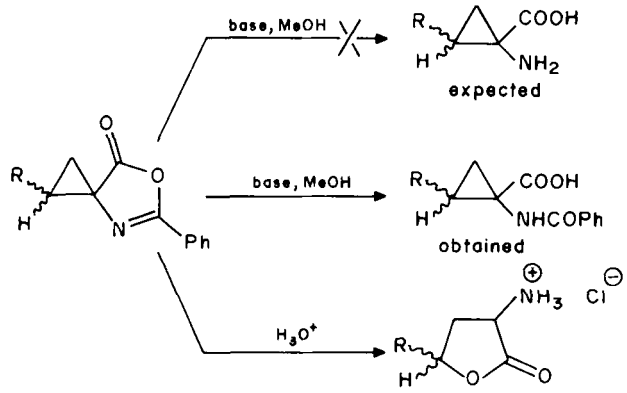


TABLE 44. Preparation of substituted 4-ethylthiobutyric acids from γ-butyrolactones, aluminum trihalide and ethanethiol

R^1	R^2	X	Rx time (h)	Yield(%)
H	H	Br	0.2	87.7
H	H	Br	1.3[a]	94.5
Et	H	Br	43.5	88
Ph	H	Br	43.5	88
Ph	H	Br	21[a]	84
H	Me	Cl	23	84.6
H	Me	Br	2	80.5
H	C_7H_{15}	Cl	37	91.3
H	C_7H_{15}	Br	13	91.2

[a]The ratio of the reactants has been varied.

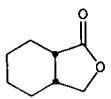
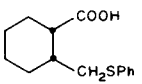
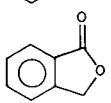
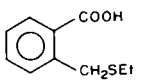
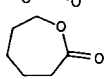
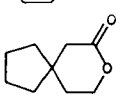
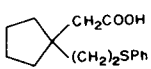


(621)

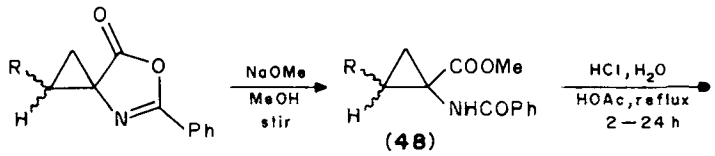
did not afford the desired product but instead led to the production of lactones by cleavage of the cyclopropane ring in the starting material.

However, the desired 1-amino-2-aryl(methyl)cyclopropanecarboxylic acids were obtained as their hydrochloride salts by the approach shown in equation 622. Thus, initial treatment of the spiroheptenes with sodium methoxide in methanol produced the 1-benzoylamino-2-aryl(methyl)cyclopropanecarboxylic acid methyl esters, which upon reaction with hydrochloric acid in aqueous acetic acid afforded the salts.

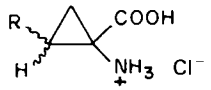
TABLE 45. Preparation of acids by reaction of lactones with aluminum trihalide and thiols[a]

Lactone	X	R	Rx temp (°C)	Rx time (h)	Acid product	Yield(%)
	Cl	Et	0	1.5	$EtS(CH_2)_2COOH$	60.4
	Cl	Ph	25	2[b,c]	$PhS(CH_2)_2COOH$	81
	Br	Ph	25	7	$PhS(CH_2)_3COOH$	53.9
	Br	Ph	25	50	$PhS(CH_2)_2C(Ph)_2COOH$	29.5
	Br	Ph	30	11		48.5
	Br	Et	25	23		9.5
	Br	Et	25	3.5	$EtS(CH_2)_4COOH$	53
	Br	Ph	Reflux	0.5	$PhS(CH_2)_4COOH$	31.4
	Br	Et	25	13	$EtS(CH_2)_5COOH$	45.3
	Br	Ph	25	240[b]		45

[a]Excess thiol used as solvent. [b]Reaction was run under nitrogen. [c]Dichloromethane was used as a cosolvent.



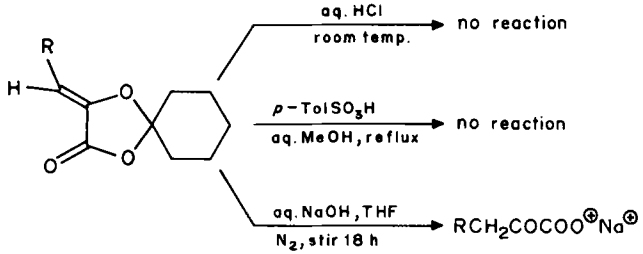
(48)



(49) (622)

R	Configuration	Yield **48**(%)	Yield **49**(%)
Ph	*E*	90	85
Ph	*Z*	90	60
p-Tol	*E*	90	80
p-Tol	*Z*	90	55
p-An	*E*	96	—
p-An	*Z*	95	28
m-An	*E*	95	76
p-ClC_6H_4	*E*	80	82
p-ClC_6H_4	*Z*	85	50
o-ClC_6H_4	*E*	90	88
Me	*E*	85	90
Me	*Z*	85	84

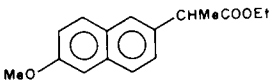
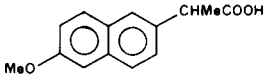
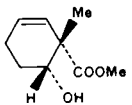
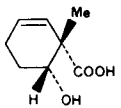
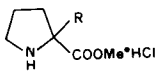
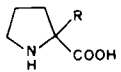
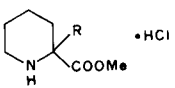
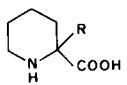
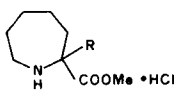
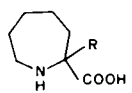
In addition to the basic hydrolysis of some common organic esters to their corresponding carboxylic acids as reported in Table 46, there have also been some reports of the basic hydrolysis of some interesting molecules. One such report[1521] involves the conversion of 5-ylidene-2,2-pentamethylene-1,3-dioxolan-4-ones to α-keto acids upon saponification (equation 623). In contrast to their stability to aqueous acid, the dioxolan-4-ones are readily hydrolyzed to α-keto acids upon treatment with aqueous sodium hydroxide in tetrahydrofuran.



(623)

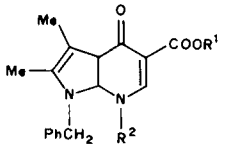
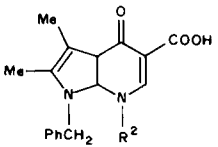
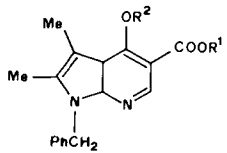
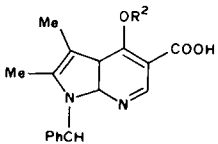
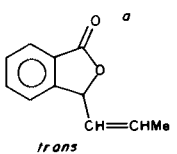
R =	*n*-Pr	*i*-Pr	Ph
% Yield =	76	73	89

TABLE 46. Basic hydrolysis of some common esters

Ester	Rx conditions	Acid	Yield (%)	Reference
p-$Me_2C{=}CHCH_2C_6H_4CHMeCOOBu\text{-}t$	1. EtOH, aq. NaOH, stir room temp., 4 h 2. HCl	*p*-$Me_2C{=}CHCH_2C_6H_4CHMeCOOH$	95.4	1517
p-$Me_2C{=}CHCH_2C_6H_4CHMeCOOEt$		*p*-$Me_2C{=}CHCH_2C_6H_4CHMeCOOH$	—	1517
p-$Me_2CHCH_2C_6H_4CHMeCOOEt$		*p*-$Me_2CHCH_2C_6H_4CHMeCOOH$	—	1517
m-$PhOC_6H_4CHMeCOOEt$		*m*-$PhOC_6H_4CHMeCOOH$	—	1517
			—	1517
	1. MeOH, 10% aq. KOH 2. H_3O^+		75	1518
	1. EtOH, aq. NaOH reflux 30 min 2. Amberlite IR 210			1519
R = Me, Ph, $PhCH_2$			72 88 79	
	1. EtOH, aq. NaOH reflux 30 min 2. Amberlite IR 210			1519
R = Me, Ph, $PhCH_2$			88 75 61	
	1. EtOH, aq. NaOH reflux 30 min 2. Amberlite IR 210			1519
R = Me, Ph, $PhCH_2$			65 89 61	

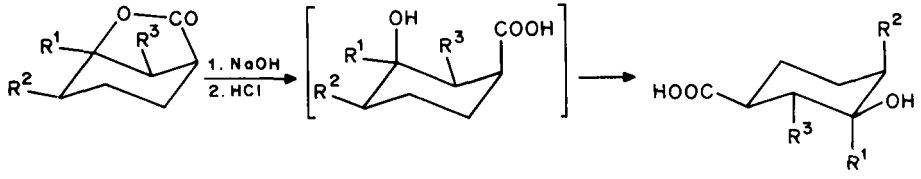
(*continued*)

TABLE 46 (*continued*)

Ester	Rx conditions	Acid	Yield (%)	Reference
	1. aq. NaOH, stir, reflux 2. HCl			1509
R^1 = Me, R^2 = Me			94	
$R^1 = R^2$ = Et			—	
	1. aq. NaOH, stir reflux 2. HCl			1509
$R^1 = R^2$ = Me			54	
$R^1 = R^2$ = Et			100	
$RCOOCH_2CN$	1. MeOH, NaOH, stir room temp. 5 h 2. HCl	RCO_2H		1520
R = Ph, cyclo-C_6H_{11}, α-Naph, *o*-Tol *m*-$O_2NC_6H_4$, cyclopropyl			89 76 79 84 93 60	
trans R = *o*-[MeOH=$CHCH_2$(OH)]C_6H_4		 *trans*	80	

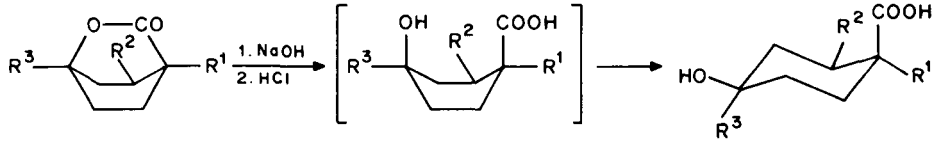
[a]Initial acid formed underwent lactonization.

Another interesting class of organic molecules which readily undergo saponification are the bicyclic γ- and δ-lactones (equations 624 and 625) which both yield[1522] *cis*-hydroxy acids upon treatment with base followed by neutralization with acid. However, if the hindered α-substituted bicyclic γ-lactone illustrated in equation 626 is subjected to the same conditions, an intermediate diaxial hydroxy acid is initially formed which recyclizes to the starting bicyclo lactone rather than rearranging to the diequatorial hydroxy acid.



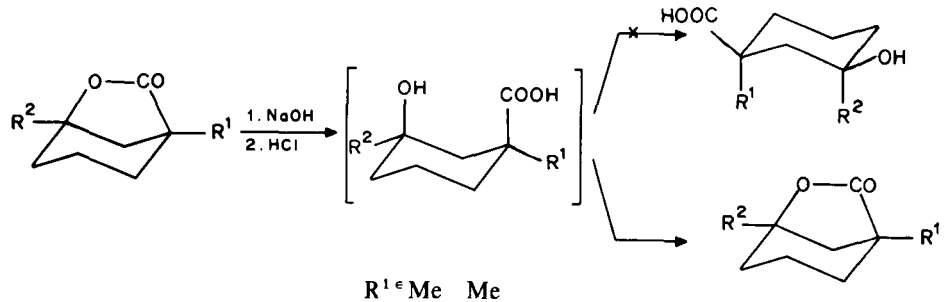
R^1 =	H	Me	H	H
R^2 =	H	H	Me	H
R^3 =	H	H	H	Me
% Yield =	98.4	94.3	94.9	96.2

(624)



R^1 =	Me	Me	Me
R^2 =	H	Me	H
R^3 =	H	H	Me
% Yield =	96.8	95.9	91

(625)

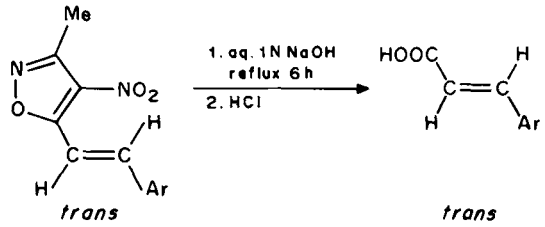


R^1 =	Me	Me
R^2 =	H	Me

(626)

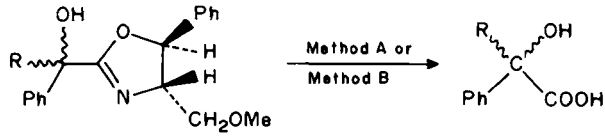
Basic hydrolysis of 3-methyl-4-nitro-5-styrylisoxazoles substituted in the phenyl ring (equation 627) gives rise to *trans*-cinnamic acids[1523] in good yields, while treatment of the similar α-substituted α-hydroxyoxazolines with either methyl iodide in base or triethyloxonium fluoroborate (equation 628) affords[1524] α-substituted α-hydroxyphenylacetic acids in which no significant racemization has occurred during hydrolysis (Table 47).

Basic hydrolysis of 4-substituted 2,2-bis(trifluoromethyl)-2*H*-oxazol-5-ones produces[1525] the corresponding α-ketocarboxylic acids in good yields (equation 629).



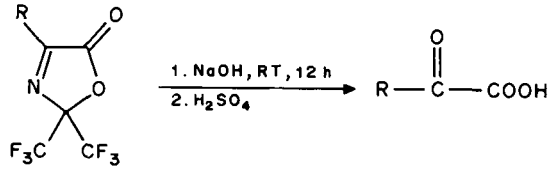
(627)

Ar =	Ph	p-ClC_6H_4	o-ClC_6H_4	m-ClC_6H_4	2,4-$Cl_2C_6H_3$	p-Tol	p-An
% Yield =	65	67	90	90	81	96	70



(628)

Method A: MeI in Me_2SO, stir at RT for 18–30 h; remove excess MeI and reflux with 2N KOH for 8 h, then cool to 0 °C and add 12N HCl.
Method B: Et_3OBF_4 in CH_2Cl_2, stir at RT overnight, add Me_2SO and 2N KOH with reflux for 8 h, then cool to 0 °C and add 12N HCl.



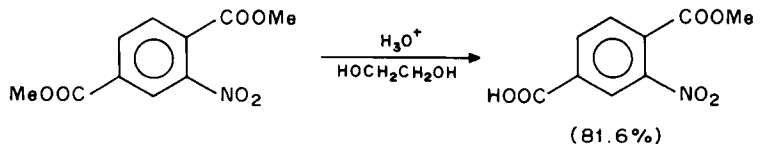
(629)

R =	Ph	$PhCH_2$
% Yield =	91	67

TABLE 47. Hydrolysis of α-substituted α-hydroxyoxazolines

R	% Yield	% ee	Configuration
Me	70–76[a]	0–47.6[a]	*R* or *S*[a]
Et	65	33.0	*S*
n-Pr	62	39.0	*S*
i-Pr	57	41.0	*S*
i-Bu	55	50.0	*S*
p-Tol	60	76.0	*S*
p-An	55	62.0	*S*
1-Naph	62	65.0	*S*
2-Thi	73	87.0	*S*

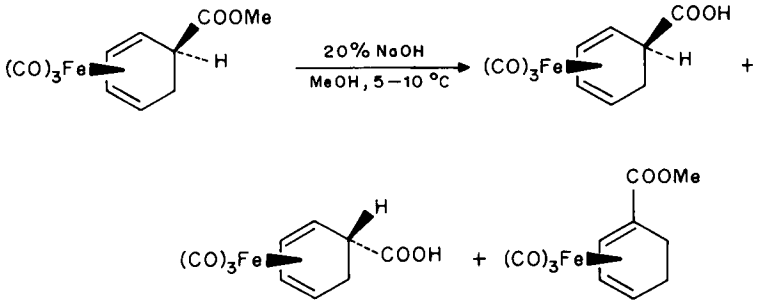
[a]Different reaction conditions afford different values for pure *R* or *S* configuration.



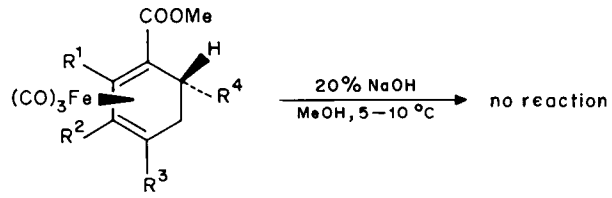
(630)

Selective hydrolysis of diesters has been reported[1526] to occur in the presence of a catalytic amount of water-miscible solvent and/or an emulsifer, as in equation 630.

An interesting approach to acquiring information concerning the steric and electronic effects on the reactivities of ester groups has been the study[1527] of the alkaline hydrolysis of a series of methoxycarbonyl derivatives of cyclohexa-1,3-diene-Fe(CO)$_3$. Whereas a methoxycarbonyl group located in the 5β- or 1-position (equations 631 and 632) of



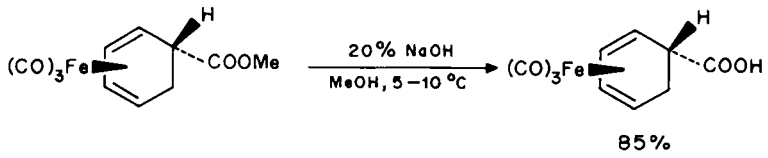
(631)



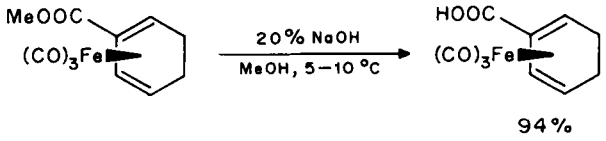
(632)

$R^1 = R^2 = R^3 = R^4 = H$
$R^1 = R^2 = R^3 = H$, $R^4 = Me$
$R^1 = R^3 = R^4 = H$, $R^2 = Me$
$R^2 = R^3 = R^4 = H$, $R^1 = OMe$
$R^1 = R^3 = R^4 = H$, $R^2 = OMe$

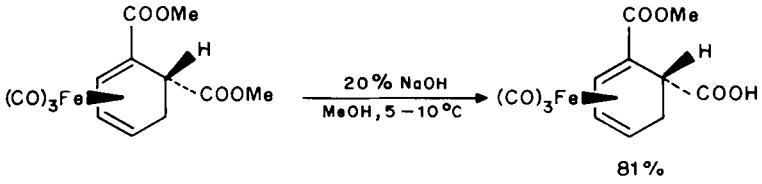
monomethoxycarbonyl derivatives of cyclohexa-1,3-diene-Fe(CO)$_3$ are resistant to saponification for steric and electronic reasons, respectively, location of these groups in the 5α- or 2-position (equations 633 and 634) of the same molecule leads, upon alkaline hydrolysis, to excellent yields of the corresponding monocarboxylic acid with substituted cyclohexa-1,3-diene dicarboxylic esters, iron tricarbonyl complexation has been used successfully[1527] to enable regiospecific half hydrolysis to occur producing the dicarboxylic monoesters, a reaction which cannot be accomplished using the parent uncomplexed



(633)

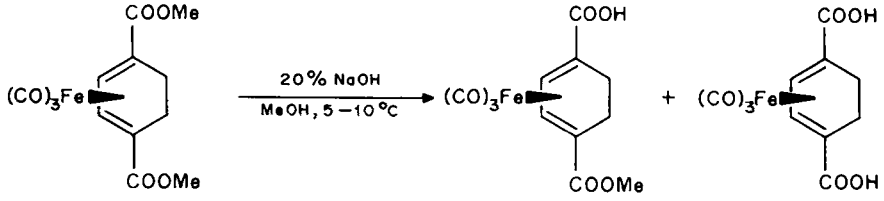


(634)



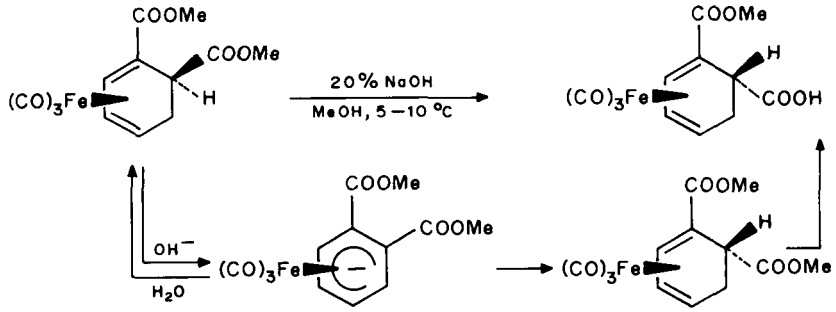
(635)

diester. For example, saponification of tricarbonyl(η^4-1,6α-dimethoxycarbonylcyclohexa-1,3-diene)iron leads to hydrolysis of the 6α-methoxycarbonyl group only (equation 635). Similar treatment of the 1,4-dimethoxycarbonyl analogue afforded a 1:1 mixture composed of the hydrolysis products of one and both methoxycarbonyl functions (equation 636) since the presence of an electron-withdrawing methoxycarbonyl substituent at the 4-position appears to enhance the rate of basic hydrolysis of the methoxycarbonyl substituent at position 1.

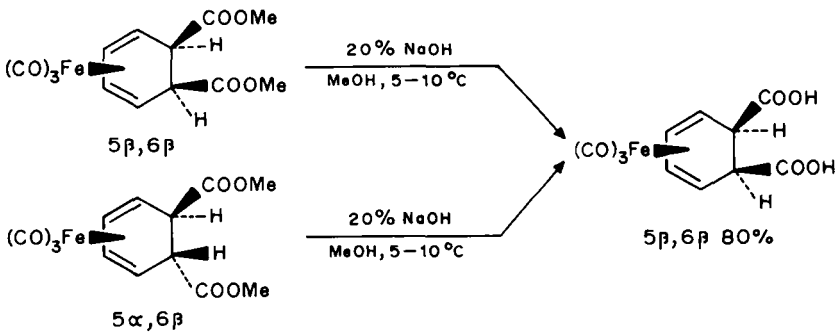


(636)

An interesting result is obtained when the 6β-analogue is subjected to the same saponification conditions as the 6α-compound reported in equation 635, when the half-ester obtained in equation 637 is the same as that obtained from the 6α-compound. Thus complete epimerization has occurred, which the authors claim is caused by formation of the carbanion shown in equation 637. Relief of steric strain causes epimerization to occur also when the 5α,6β-analogue (equation 638) is treated similarly. The best example of the specific preference of hydrolysis for an α-methoxycarbonyl group over a



(637)



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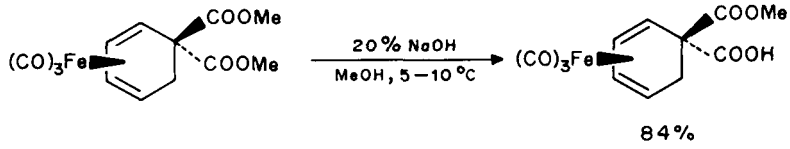
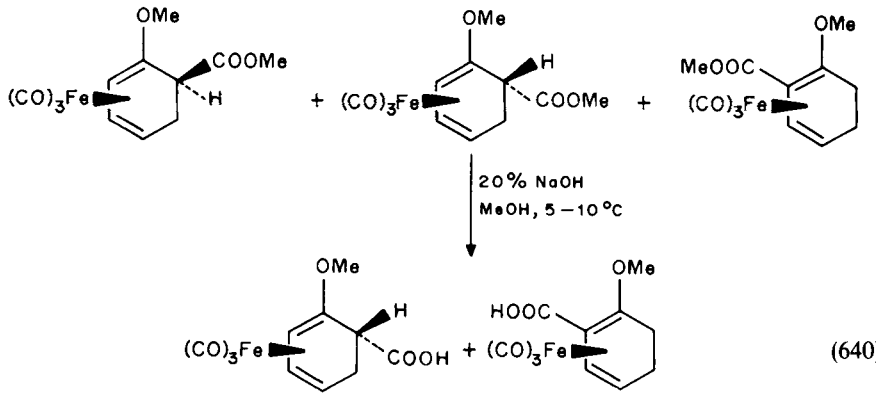


(639)

β-methoxycarbonyl located group in these iron tricarbonyl complexed diesters is illustrated (equation 639) by the results obtained upon saponification of tricarbonyl-(η^4-5α,5β-dimethoxycarbonylcyclohexa-1,3-diene) iron.

To test the effect upon epimerization of different substituents placed at various positions in the monomethoxycarbonyliron tricarbonyl compounds, a series of saponification reactions were performed[1527] starting with the base catalyzed hydrolysis of a 5:6:9 mixture consisting of the three compounds shown (equation 640). From the 1:1 product mixture obtained it appears that a functional group located at the 1-position promotes epimerization in these molecules through the relief of steric strain, while, in contrast, replacing the hydrogen atom on the methoxycarbonyl bearing carbon with some other group prevents epimerization (equation 641) and with certain substituents (equations 642 and 643) the saponification reaction itself is prevented.

Since esters are often used to protect acid functions while structural changes in the rest



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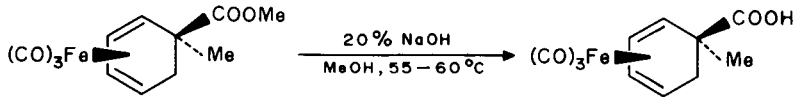

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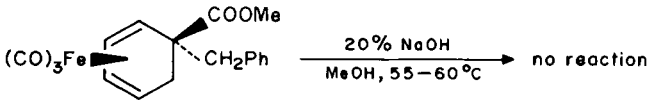

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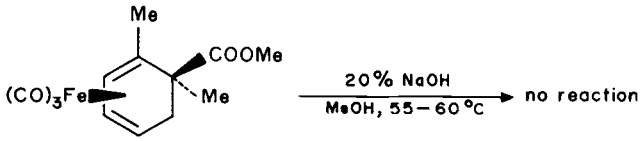


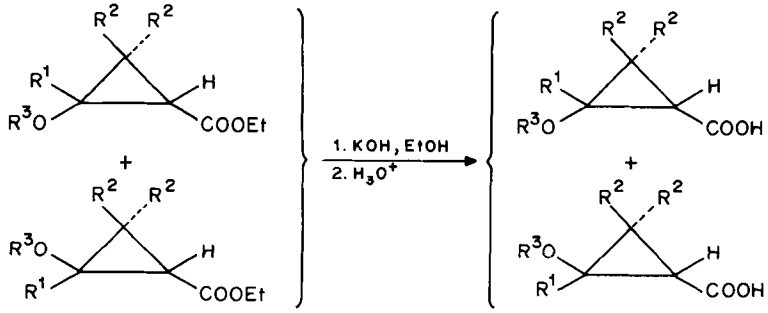
(643)

of the molecule are accomplished, it is very important that any conformational or chiral features built into the ester be retained during hydrolysis to the free acid. Several examples of this type of concern during ester hydrolysis have been reported in the recent literature, as in the preparation[1528] of optically pure 3-hydroxyalkanoic acids of known configuration by saponification (equation 644) of their methyl esters. Saponification of (*Z*/*E*)-2-alkoxycyclopropanecarboxylic esters also affords[1529] the corresponding (*Z*/*E*)-2-alkoxycyclopropanecarboxylic acids (equation 645) which show stereomutation in water–methanol solution (equation 646). At higher temperatures the water–methanol solution was observed to cause ring opening to produce the corresponding γ-ketocarboxylic acids (equation 647) in quantitative yield according to the mechanism shown.

Configurationally specific isomers of β-substituted alkanoic acid have been prepared[1530] in excellent yields by the basic hydrolysis (equation 648) of the esters of

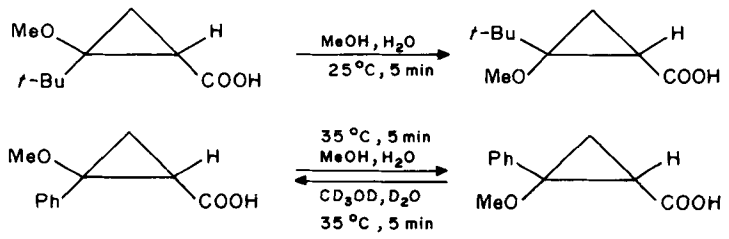
$$Me(CH_2)_nCH(OH)CH_2COOMe \xrightarrow[2.\ H_3O^+]{1.\ NaOH} Me(CH_2)_nCH(OH)CH_2COOH \quad (644)$$

n	Configuration of acid and ester	Yield (%)
0	*R*	70
0	*S*	70
6	*R*	79
6	*S*	75.8
8	*R*	80.1
8	*S*	79.8
10	*R*	79.7
10	*S*	81.5
12	*R*	82.1
12	*S*	81.2

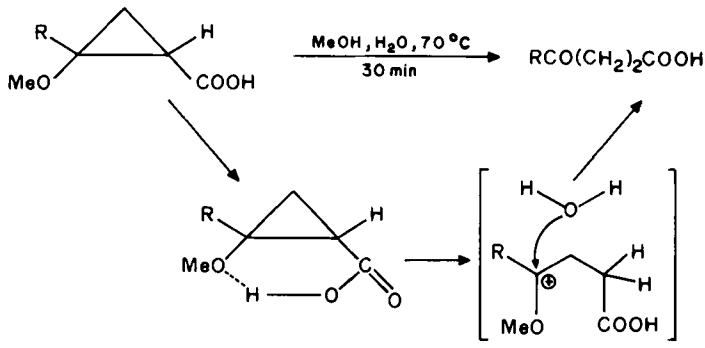


(645)

R^1	R^2	R^3	Configuration of ester	Configuration of acid	% Yield
Ph	H	Me	*Z*	7:1(*Z*:*E*)	95
Ph	H	Me	*E*	*E*	90
Ph	H	Et	1:1(*Z*:*E*)	1:1(*Z*:*E*)	93
Ph	Me	Me	1:1(*Z*:*E*)	1:1(*Z*:*E*)	90
3,4-$(MeO)_2C_6H_3$	H	Me	1:1(*Z*:*E*)	*Z*	85
i-Pr	H	Me	1:1(*Z*:*E*)	1:1(*Z*:*E*)	85
t-Bu	H	Me	1:1(*Z*:*E*)	8:1(*Z*:*E*)	84

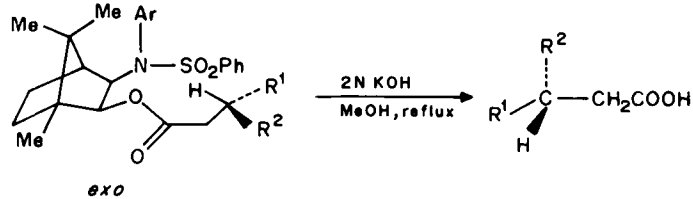


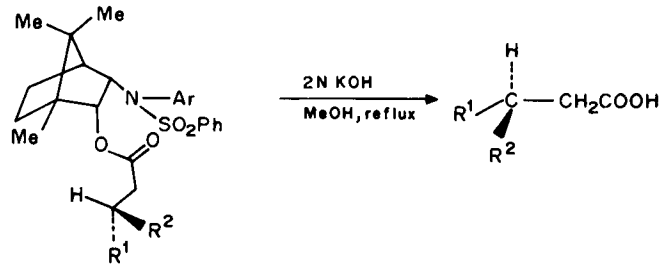
(646)



(647)

R = Ph, 3,4-$(MeO)_2C_6H_3$, *i*-Pr, *t*-Bu





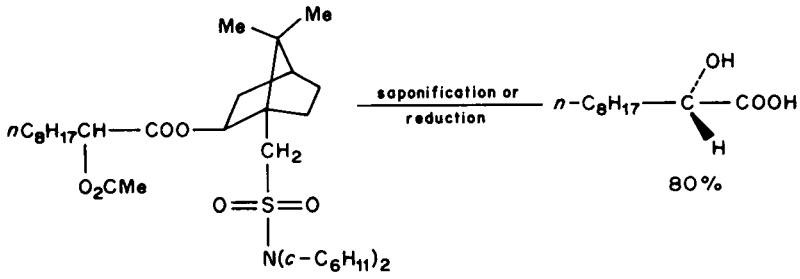
(648)

Ar = 3,5-$Me_2C_6H_3$

R^1	R^2	Configuration of acid from *exo* adduct	*endo* adduct
Me	Et	—	—
Me	*i*-Pr	—	—
Et	Me	—	—
Et	*i*-Pr	*S*	*R*
i-Pr	Me	—	—
i-Pr	Et	*R*	*S*
Me	vinyl	*S*	*R*
Me	Ph	*S*	*R*
Me	*p*-Tol	—	*R*

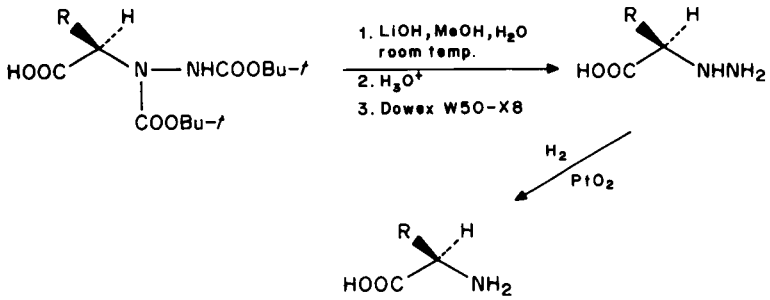
sulfonamide-shielded *exo*- and *endo*-borneol. Similarly structured α-acetoxy esters have been either saponified or reduced (equation 649) to produce[1531] α-hydroxy acids in high enantiomeric purity. Excellent yields of α-hydrazino acids of ⩾98% optical purity and specific absolute configuration have been obtained[1532] upon saponification (equation 650) of the corresponding α-hydrazinoesters. Hydrogenolysis of the α-hydrazino acids using H_2/PtO_2 gives the corresponding α-amino acids also in excellent yields.

Although chemical yields in the 70% range have been reported[1533] during the basic hydrolysis of α-alkyl-α-hydroxy-α-phenyl esters of (−)-menthol, the α-alkyl mandelic acid products were obtained in only modest enantiomeric excess (ee) (equation 651).



(649)

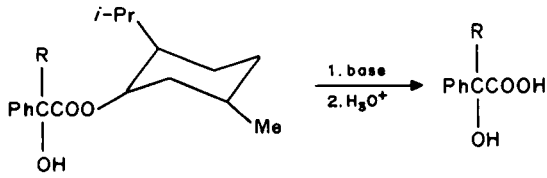
saponification conditions: K_2CO_3, MeOH, 20 °C, 20 h
reduction conditions: $LiAlH_4$, Et_2O, 20 °C, 1 h, then 1N aqueous HCl



(650)

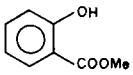
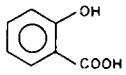
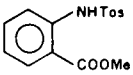
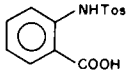
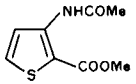
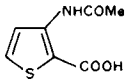
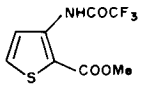
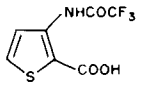
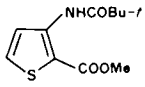
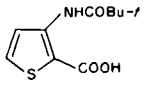
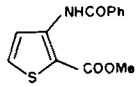
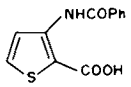
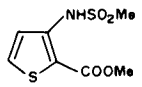
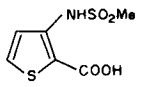
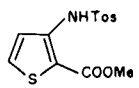
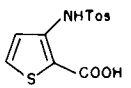
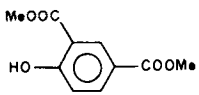
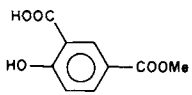
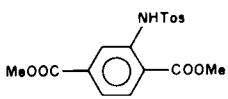
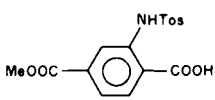
R = Me	$PhCH_2$	Me_2CHCH_2	$MeCH_2$	$Me(CH_2)_3$
% Yield (hydrazino acid)[a] = 78	81	81	65	78
% Yield (amino acid)[a] = 92	89	91	80	90

[a]All products had *R* absolute configuration and ⩾98% ee.



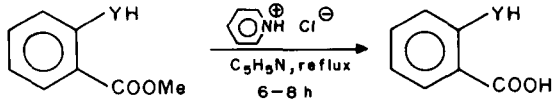
(651)

TABLE 48. Pyridinium chloride catalyzed ester hydrolysis[1534]

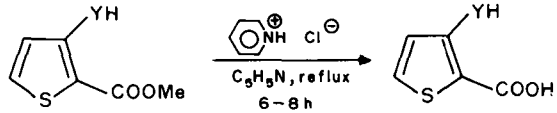
Ester	Product	Yield (%)
		76
		89
		51[a]
		67
		80
		83[b]
		100
		78
		80[c]
		79[c]

[a]Mixture refluxed for 22 hours.
[b]Mixture refluxed for 30 hours.
[c]Pyridine used alone.

Hydrolysis of the methyl esters of benzoic acids (equation 652) or thiophene-2-carboxylic acids (equation 653) has been accomplished[1534] in yields of 51 to 100 percent by refluxing the esters with pyridinium chloride in pyridine (Table 48), but the presence of an acid substituent *ortho* to the methoxycarbonyl group was found to be essential for the reaction to proceed.

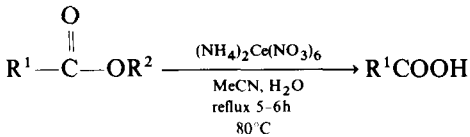


(652)



(653)

Benzoate and phenylacetate esters have been[1535] oxidatively cleaved to the corresponding carboxylic acid (equation 654) by ceric ammonium nitrate in aqueous acetonitrile in 56 to 85 percent yields (Table 49).



(654)

TABLE 49. Ceric ammonium nitrate cleavage of esters[1535]

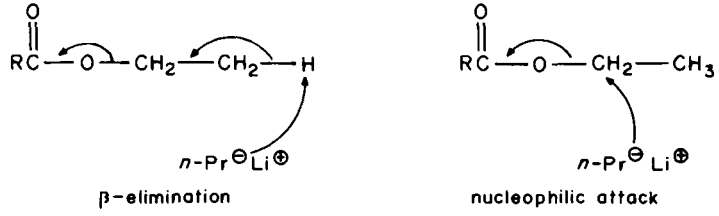
R^1	R^2	Yield (%)
Ph	Me	56
Ph	Et	59
Ph	*n*-Pr	61
p-ClC_6H_4	Et	58
m-ClC_6H_4	Et	58
p-$O_2NC_6H_4$	Et	62
p-BrC_6H_4	Et	65
Ph	$CH_2CH{=}CH_2$	78
p-ClC_6H_4	$CH_2CH{=}CH_2$	74
m-ClC_6H_4	$CH_2CH{=}CH_2$	70
p-$O_2NC_6H_4$	$CH_2CH{=}CH_2$	70
p-Tol	$CH_2CH{=}CH_2$	69
p-An	$CH_2CH{=}CH_2$	85
Ph	CH_2Ph	64
p-ClC_6H_4	CH_2Ph	65
p-Tol	CH_2Ph	70
$PhCH_2$	Et	68
$PhCH_2$	*n*-Pr	65

The catalytic activity of several nucleic acid bases and the polymers containing these bases as pendant groups of the polymer chain have been examined for their effectiveness in the saponification of carboxylic acid esters in aqueous alkali medium. It was found[1536] that the saponification velocity of 4-nitrophenyl acetate in a buffer solution of pH 8.2 at 25 °C was increased by about 1000 times or more by addition of the base in comparison with the reaction in the absence of base. The accelerating effect by the bases investigated was reported[1536] to be in the following order: adenine < N^6,N^6-dimethyladenine < 6-methylpurine < N^6-acetyladenine < purine < poly(uridylic acid) < poly(adenylic acid) < poly(9-vinyladenine) < poly(9-vinyl-N^6-acetyladenine). It appears that the catalytic effect of these bases is largely influenced by their solvolysis in water or by their basicity.

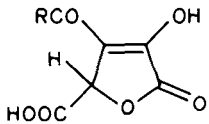
Although not a hydrolysis reaction, one of the more novel approaches to the preparation of hindered aliphatic acids involves[1537] a facile dealkylation which occurs when the corresponding ester is treated (equation 655) with *n*-propyllithium in ether at 0 °C. The authors propose two mechanisms, the first involving β-elimination and the second involving nucleophilic attack on the α-carbon of the ester group.

$$R^1R^2R^3CCOOR \xrightarrow[2.\ H_2O,\ HCl]{1.\ n\text{-PrLi, ether, Ar, 0 °C, stir, 36 h}} R^1R^2R^3CCOOH \qquad (655)$$

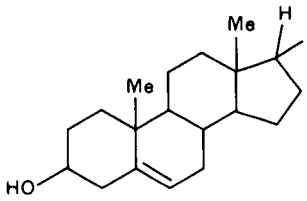
R^1	R^2	R^3	R	Yield (%)
t-Bu	*i*-Pr	Et	Et	61
t-Bu	Et	Et	Et	44
t-Bu	*i*-Pr	Me	Et	77
t-Bu	*i*-Pr	Me	Me	39
t-Bu	*i*-Pr	Me	*t*-Bu	82
t-Bu	*i*-Pr	Me	n-C_8H_{17}	72
i-Pr	*i*-Pr	*i*-Pr	Et	53
i-Pr	*i*-Pr	Et	Et	42
i-Pr	*i*-Pr	Me	Et	72



Another novel approach to the preparation of carboxylic acids is the zinc-catalyzed[1538] elimination of the oxalyl moiety from 4-carboxy-2-hydroxybutenolides (equation 656) to produce 2-hydroxy-4-keto acids.



$$\xrightarrow[NaOH,\ 65\ °C]{Zn(OAc)_2} RCOCH_2CH(OH)COOH \qquad (656)$$

R	Rx time (h)	Yield (%)
Me	1.5	76
i-Pr	2	87
i-Bu	2	84
Ph	1	83
OEt	1.5	86
	5	45

Asymmetric enzymatic hydrolysis has been employed to produce[1539] optically active acids from their corresponding racemic esters as illustrated in the general equation 657.

$$R^1COS(CH_2)_nCHR^2COOR^3 \xrightarrow[\text{buffer}]{\text{enzyme}} R^1COS(CH_2)_nCHR^2COOH \qquad (657)$$

One of the most interesting reactions reported[1540] for the hydrolysis of carboxylic acid esters involves ultrasound. Immersion of an ultrasonic probe, at a frequency of 20,000 hertz, into a two-phase reaction mixture composed of the ester and 20% aqueous sodium hydroxide for the time interval specified assists ester hydrolysis (equation 658). The principal effect of applying ultrasound to the reaction mixture was, according to the authors, not due to macroscopic heating but to the secondary cavitation effect of emulsification.

$$R^1COOR^2 + 20\%\,\text{aq. NaOH} \xrightarrow[\text{no heat}]{\text{ultrasound}} R'COOH \qquad (658)$$

Ester	90 min, reflux	10 min, room temp., ultrasound	60 min, room temp., ultrasound	10 min, oil bath, 100 °C	10 min, oil bath, 120 °C
	% Isolated Yield of Acid with				
PhCOOMe	97	98	—	13	77
2,4,6-$Me_3C_6H_2COOMe$	0	0	0	—	—
2,4-$Me_2C_6H_3COOMe$	15	15	94	4	—
3,5-$Me_2C_6H_3COOMe$	71	62	96	10	—

**2. Hydrolysis of nitriles*

Examples from the recent literature again demonstrate that both basic and acidic conditions can be used to hydrolyze nitriles.

An example of basic hydrolysis involves the conversion[1517] of α-arylpropionitriles (equation 659), in excellent yields, to α-arylpropionic acids using methanolic sodium

hydroxide. Treatment of the higher homologues of 2,2-disubstituted hydroxybutyronitriles with sodium hydroxide in ethylene glycol produces[1541] (equation 660) the corresponding hydroxy acids in excellent yields.

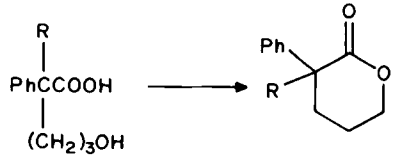
$$\mathrm{ArCHMeCN} \xrightarrow[\text{2. HCl}]{\text{1. NaOH,MeOH,N}_2,\ \text{reflux overnight}} \mathrm{ArCHMeCOOH} \tag{659}$$

$\mathrm{Ar} = p\text{-}\mathrm{Me_2C{=}CHCH_2C_6H_4}$, Ph, $p\text{-}\mathrm{PhOC_6H_4}$, α-Naph

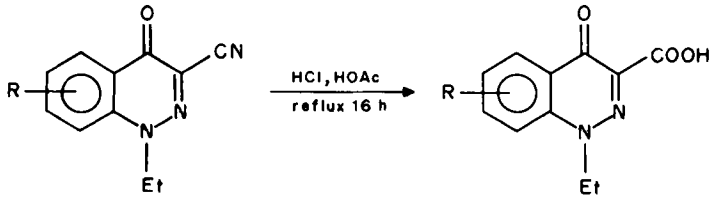
$$\mathrm{PhCCN} \xrightarrow[\text{glycol}]{\mathrm{OH^{\ominus}}} \mathrm{Ph{-}C{-}COOH} \tag{660}$$

R	n	Yield (%)
Ph	3	90[a]
$PhCH_2$	3	85[a]
Et	3	92[a]
Ph	4	91
$PhCH_2$	4	90
Ph	5	89
$PhCH_2$	5	90
Et	5	85
Ph	6	88
$PhCH_2$	6	86

[a]These hydroxy acids cyclize to lactones as shown below



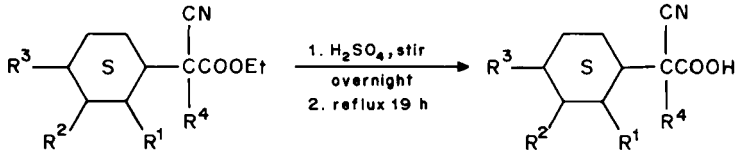
Acidic hydrolysis conditions have been used to convert a variety of nitriles to their corresponding carboxylic acids, including substituted cinnolinones[1542] to cinnolin-3-carboxylic acids (equation 661).



(661)

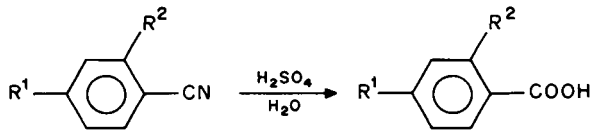
R =	H	6-Me	7-MeO	7-CN
% Yield =	92	92	26	51 (diacid)

Sulfuric acid catalyzed hydrolysis[1543] of substituted cyclohexane-1-α-cyanoacetates produces (equation 662) the corresponding acids, while similar hydrolysis[1544] of substituted benzonitriles leads to excellent yields of the corresponding substituted benzoic acids (equation 663). In the same article[1544] the basic hydrolysis of similarly substituted benzaldehyde oximes (equation 664) was reported to give moderate yields of the corresponding substituted benzoic acids.



(662)

R^1	R^2	R^3	R^4
Me	H	H	Me (45%)
Me	H	H	Et
Me	H	H	*i*-Pr
Me	H	H	$CH_2CH{=}CH_2$
Me	H	H	$PhCH_2$
Me	H	H	CH_2COOH
H	Me	Me	H
H	Me	Me	Et
H	Me	Me	*n*-Pr
H	Me	Me	$PhCH_2$
H	Me	Me	CH_2COOH
H	Me	Me	CH(Me)COOH

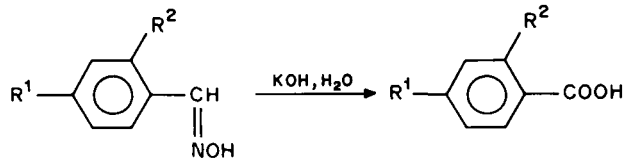


(663)

$R^1 = H \quad NO_2$

$R^2 = Cl \quad NO_2$

% Yield = 82 90



(664)

$R^1 =$ Cl Br

$R^2 =$ H H

% Yield = 56 62

Hydrochloric acid has been used to hydrolyze a variety of nitriles to carboxylic acids including 4-nitrozaalkanonitriles to nitrazaalkanoic acids[1545] (equation 665), *N*-benzoylaminoacrylic acid cyanides to 3-(*N*-benzoylamino)-3-substituted pyruvic acids[1546] (equation 666), and α-cyanoimines to α-keto acids[1547] (equation 667).

$$\underset{\text{O}_2\text{NNCH}_2\text{CH}_2\text{CN}}{\overset{\text{R}}{|}} \xrightarrow{\text{HCl},\text{H}_2\text{O}} \underset{\text{O}_2\text{NNCH}_2\text{CH}_2\text{COOH}}{\overset{\text{R}}{|}} \qquad (665)$$

R = Me; Et

% Yield = 67; 81

$$\underset{\text{RCH=CCCN}}{\overset{\text{O}}{\overset{\|}{\underset{|}{\underset{\text{NHCPh}}{\overset{\|}{\underset{\text{O}}{}}}}}}} \xrightarrow[\text{reflux 15–20 min}]{20\%\,\text{HCl}} \underset{\text{RCH=CCCOOH}}{\overset{\text{O}}{\overset{\|}{\underset{|}{\underset{\text{NH—C—Ph}}{\overset{\|}{\underset{\text{O}}{}}}}}}} \qquad (666)$$

R =	Ph	*p*-An	PhCH=CH	*o*-HOC_6H_4	*p*-HOC_6H_4
% Yield =	62	48	39	36	36

R =	*p*-$Me_2NC_6H_4$	3,4-$(MeO)_2C_6H_3$	piperidino	*o*-An
% Yield =	28	64	60	54

R =	indolo	furfuralo
% Yield =	52	57

$$\underset{\text{RC=NPh}}{\overset{\text{CN}}{|}} \xrightarrow[\text{reflux 3 h}]{\text{conc. HCl, acetone}} \underset{\text{RCCOOH}}{\overset{\text{O}}{\|}} \qquad (667)$$

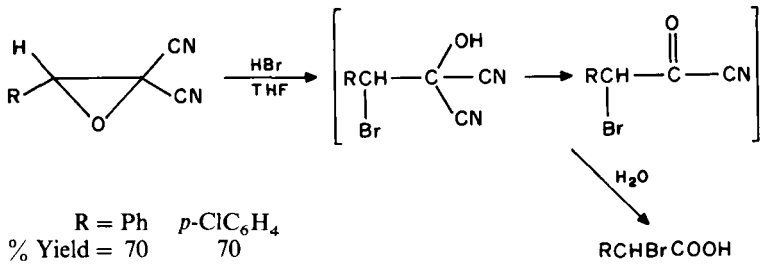
R =	PhCH=CH	*o*-$O_2NC_6H_4CH$=CH	Ph	*p*-HOC_6H_4	*p*-ClC_6H_4
% Yield =	75	71	81	84	85

Treatment of dicyano compounds normally leads to the corresponding dicarboxylic acid, as in the case of the preparation[1548] of succinic, glutaric and adipic acids (equation 668) labeled with carbon-14. However, if the two cyano groups are *gem* and attached to the carbon atom of an epoxide, then the corresponding α-halo substituted monocarboxylic acids are produced[1549] (equation 669).

$$\text{NC}^{14}(\text{CH}_2)_n\text{C}^{14}\text{N} \xrightarrow{\text{conc. HCl}} \text{HOOC}^{14}(\text{CH}_2)_n\text{C}^{14}\text{COOH} \qquad (668)$$

$n = 2, 3$ and 4

Carboxylic acids of high purity have reportedly[1550] been prepared by the gas-phase treatment of nitriles with water in the presence of a solid acid catalyst which produces a gaseous effluent containing the corresponding carboxylic acid. By this method the nitriles



R = Ph p-ClC_6H_4
% Yield = 70 70

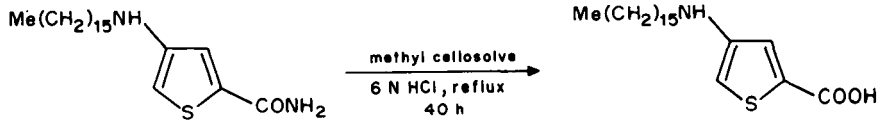
(669)

are converted to the acids more quicky and at lower pressures than with conventional liquid hydrolysis.

Polynitriles have been both hydrolyzed[1551] to polyacids of benzophenone and diphenyl oxide, and treated with microorganisms[1552,1553] containing a nitrilase system which selectively hydrolyzes only one of the cyano groups to the corresponding carboxylic acid.

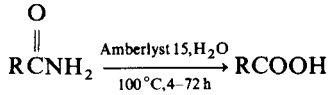
*3 *Hydrolysis of amides*

Examples of the hydrolysis of primary amides to the corresponding carboxylic acids include the acid hydrolysis[1554] of 2-carbamyl-4-hexadecylaminothiophene to 4-hexadecylamino-2-thiophenecarboxylic acid (equation 670), and a mild, selective conver-

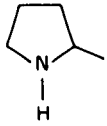


(670)

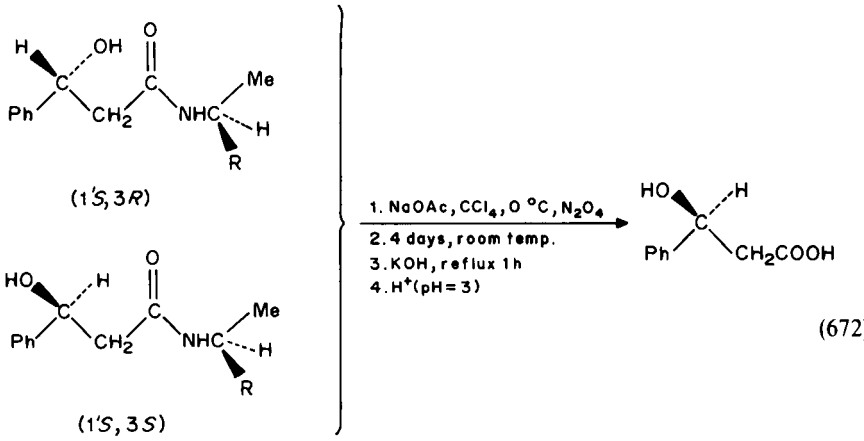
sion[1555] of unsubstituted carboxamides (equation 671). The indication of the mildness and selectivity of this approach is illustrated by the conversion of glycyl-DL-asparagine to glycyl-DL-aspartic acid by the selective hydrolysis of the unsubstituted carboxamide group in the presence of the peptide bond which is left intact.



(671)

R	Reflux time (h)	Yield (%)
$PhCH_2$	4	89
 (L)	72	90
$H_3\overset{\oplus}{N}CH_2CONHCHCH_2$ (DL)  COOH	24	95

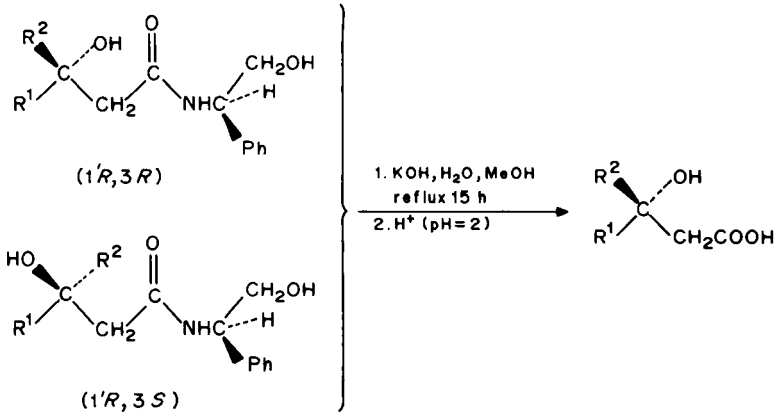
An example of the hydrolysis of secondary amides to the corresponding carboxylic acids is illustrated by the conversion[1556] of chiral mixtures of (1′*S*, 3*R*)- and (1′*S*, 3*S*)-3-hydroxy-3-phenyl-*N*-(1-substituted) propionamides to (*R*)-3-hydroxy-3-phenylpropionic acids (equation 672), and by the conversion[1556] of chiral mixtures of (1′*R*, 3*R*)- and (1′*R*, 3*S*)-3-hydroxy-*N*-(2-hydroxy-1-phenylethyl)-3-substituted propionamides to 3-hydroxy-3-substituted propionic acids (equation 673), in yields ranging from 75 to 85%.



(672)

R = Ph; β-Naph

% Yield = 80; 85

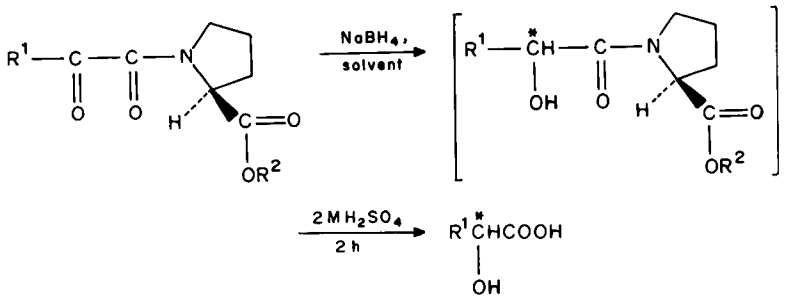


(673)

R^1 =	Ph	Me_3C	Me_2CH	n-C_3H_7	Ph
R^2 =	H	H	H	H	Me

The hydrolysis of tertiary amides is represented[1557] by the hydrolysis of the α-hydroxyamide reduction products obtained from the diastereoselective reduction of chiral α-ketoamides using sodium borohydride (equation 674). Even though the α-

hydroxyamide reduction products were not isolated, their hydrolysis with sulfuric acid afforded the corresponding optically active α-hydroxyacids in good enantiomeric excesses (Table 50).

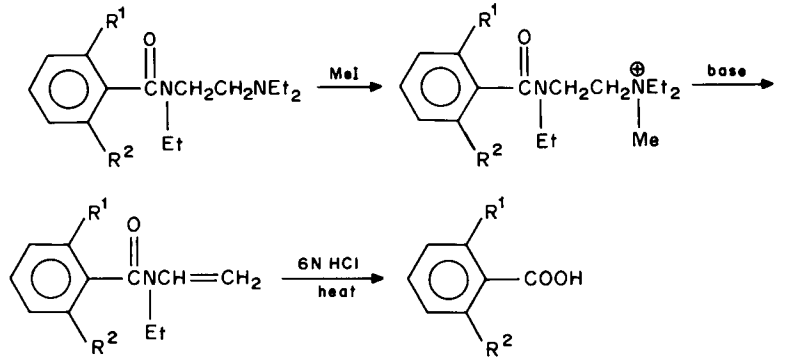


(674)

TABLE 50. Hydrolysis of α-hydroxamide reduction products obtained from reduction of α-ketoamides

R^1	R^2	Solvent	% ee	Yield (%)
Ph	Me	THF–1% H_2O	45	82
Ph	Et	THF–1% H_2O	37	29
Ph	*i*-Pr	THF–1% H_2O	46	57
Ph	$PhCH_2$	THF–1% H_2O	37	35
i-Bu	Me	THF–1% MeOH	56	59
i-Bu	*t*-Bu	THF–1% MeOH	60	82
Me	Me	THF–1% MeOH	55	41

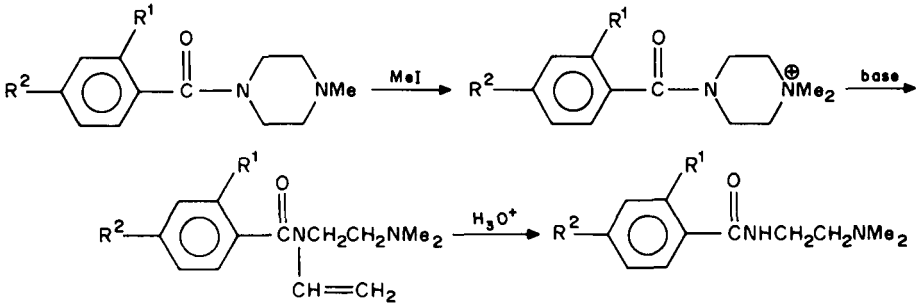
An interesting report[1558] of the conversion of tertiary amides to carboxylic acids involves the hydrolysis of the enamides derived from substituted benzamides. The overall reaction is a three step–one pot synthesis of aromatic acids which involves methylation, elimination and, finally, hydrolysis of the intermediate enamides to afford the substituted aromatic acids (equation 675). The intermediates involved in the reaction were not



(675)

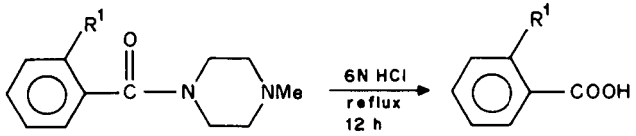
R^1 =	Me	*n*-Bu	Me
R^2 =	H	H	OMe
% Yield =	82	53	77

isolated, and the yields reported are those of the aromatic acids produced. A similar three step–one pot approach to the preparation of substituted benzoic acids using *N*-aroyl-*N'*-methylpiperazines (equation 676) has also been reported by the same authors, however a more convenient one-step conversion (equation 677) has been reported[1558] to be effective with these starting materials.



(676)

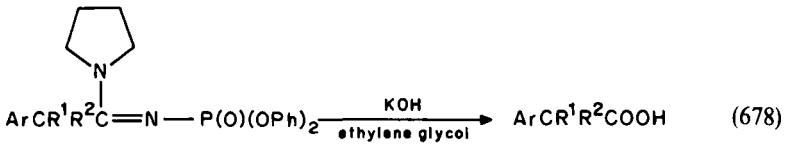
R^1 =	*n*-Bu	Me
R^2 =	H	OMe
% Yield =	73	51



(677)

R^1 =	Me	*n*-Bu
% Yield =	90	53

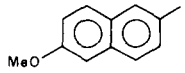
An effective method for the preparation, in excellent yields, of α-arylalkanoic acids including the nonsterodial antiinflammatory agents ibuprofen and naproxen, is the basic hydrolysis (equation 678) of *N*-phosphorylated amidines[1559,1560] in ethylene glycol (Table 51).



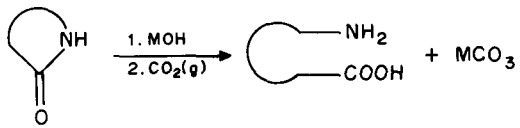
(678)

ω-Aminoalkanoic acids may be prepared[1561] by the hydrolysis of C_{5-13} lactams in the presence of lithium, calcium or barium hydroxide and carbon dioxide (equation 679). The carbon dioxide serves to precipitate the metal in the form of its carbonate.

TABLE 51. Basic hydrolysis of *N*-phosphorylated amidines

R^1	R^2	Ar	Yield (%)
Me	H	Ph	91
Et	H	Ph	91
Me	Me	Ph	100
Allyl	H	Ph	91
Me	H	2-Dibenzofuranyl	92
Me	H	p-$Me_2CHCH_2C_6H_4$	79[a]
Me	H		83[b]

[a]Ibuprofen.
[b]Naproxen.



(679)

M = Li, Ca or Ba

Copper-catalyzed cleavage of acylhydrazines has been reported[1562,1563] to produce the corresponding carboxylic acids. Using copper acetate[1562] for this conversion requires that the reaction be performed (equation 680) in the presence of oxygen, whereas by using copper chloride, the conversion can be effected[1563] without the use of oxygen (equation 681).

$$RCNHNH_2 + Cu(OAc)_2 \cdot H_2O \xrightarrow[H_2O,r.t.]{O_2,solvent,} RCOOH \quad (680)$$

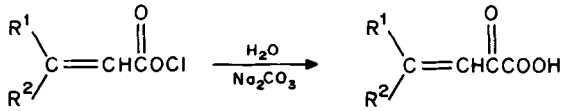
R	Solvent	Yield (%)
n-C_7H_{15}	THF	98
Ph	THF	96
Ph	MeOH	95
o-Tol	MeOH	89
m-Tol	MeOH	82
p-Tol	MeOH	86
p-An	MeOH	94
p-ClC_6H_4	MeOH	92
p-$O_2NC_6H_4$	MeOH	40

$$R^1CNHNHR^2 + CuCl_2 \cdot 2H_2O \xrightarrow[\substack{r.t.,stir\\18-20h}]{THF,H_2O} R^1COOH \quad (681)$$

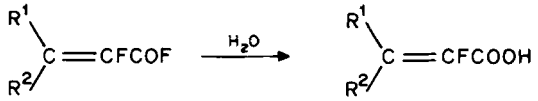
R^1	R^2	Yield (%)
Ph	H	75
$PhCH_2$	H	85
n-$C_{15}H_{31}$	H	95
Ph	OTs	95
$PhCH_2CH_2$	OTs	85
n-$C_{15}H_{31}$	OTs	80

*4. *Hydrolysis of acyl halides and anhydrides*

Recent examples of the preparation of carboxylic acids via hydrolysis of acyl halides have mainly been concerned with the preparation of unsaturated molecules. Two representative approaches are the preparation of 2-keto-3-alkenoic acids (Table 52) by the hydrolysis of α-keto-β,γ-unsaturated acid chlorides[1564] (equation 682), and the preparation of α-fluoro-α,β-unsaturated acids by the hydrolysis (equation 683) of the corresponding acid fluoride[1565].



(682)



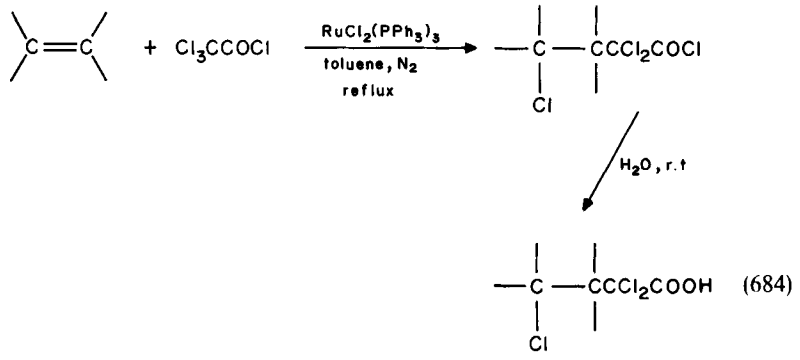
(683)

R^1 = Ph Me Ph
R^2 = Me Me H

TABLE 52. Hydrolysis of α-keto-β,γ-unsaturated acid chlorides

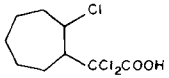
R^1	R^2	Reaction time	Z/E ratio	Yield (%)
PhS	PhS—	40 min	—	82
p-MeC_6H_4S	p-MeC_6H_4S—	10 min	—	92
p-ClC_6H_4S	p-ClC_2H_4S—	6.3 h	—	~100
PhS	Ph—	18 h	1	11
PhS	Me—	45 min	0.7	62
PhS	H	6 h	1	27
p-$TolSO_2NTol$-p |	H	1 h	Pure E	89

Hydrolysis of α,α,γ-trichloro acid chlorides, prepared by addition of trichloroacetyl chloride to olefinic compounds catalyzed by dichlorotris(triphenylphosphine) ruthenium(II), affords[1566] (equation 684) α,α,γ-trichloroalkanoic acids (Table 53).



(684)

TABLE 53. Hydrolysis of α,α,γ-trichloro acid chlorides

Acid products	Hydrolysis reaction time (min)	Yield (%)
n-$C_6H_{13}CHClCH_2CCl_2COOH$	1	99
n-$C_8H_{17}CHClCH_2CCl_2COOH$	1	99
$PhCHClCH_2CCl_2COOH$	1	97
	120	98

*5. *Hydrolysis of trihalides*

Hydrolysis of telomers of chlorotrifluoroethene, all of which contain a trichloromethyl group, produce[1567] mixtures of mono- and dicarboxylic acids (equation 685). In the presence of mercuric oxide the amounts of monoacids formed are significantly increased. Similar hydrolysis of α,α,α-trichloro-ω-esters produces[1568] α,ω-dioic acids (equation 686), since the severity of the reaction conditions (Table 54) causes hydrolysis of both the trichloromethyl and the ester functions.

$$Cl(CFClCF_2)_nCCl_3 \xrightarrow[H_2SO_4]{\text{fuming}} Cl(CFClCF_2)_nCOOH + HOOC(CFCl)_{n-1}(CF_2)_nCOOH \quad (685)$$

$n = 1, 2$ or 3

$$Cl_3CCH_2CR^1Cl(CH_2)_nCOOR^2 \xrightarrow{\text{hydrolysis}} HOOCCH_2CR^1Cl(CH_2)_nCOOH \quad (686)$$

TABLE 54. Hydrolysis of α,α,α-trichloro-ω-esters

R^1	R^2	n	Hydrolysis conditions	Yield (%)
H	Me	0	Anhydrous $FeCl_3$, stir 53 °C for 1.5 h	69
Me	Me	0	As above, stir 2 h	92
H	Me	1	P_2O_5, fuming HNO_3, stir 0.5 h at 60 °C, then 18 h at 75 °C	58
H	H	8	P_2O_5, fuming HNO_3, stir 2 h at 80 °C	92

As reported previously, base-catalyzed condensation of aromatic aldehydes with chloroform produces aryltrichloromethylcarbinols, which can then be hydrolyzed by alcoholic base to give α-alkoxyaryl acids. This approach has been used with aliphatic aldehydes[1569] to produce α-methoxyaliphatic acids (equation 687). By the use of triethylbenzylammonium chloride (TEBA) and phase transfer catalysis conditions, this approach has also been extended to aliphatic[1570] and aromatic[1571] ketones (equation 688) as well (Table 55).

$$\mathrm{RCHO + HCCl_3} \xrightarrow[\text{2. NaOH, MeOH}]{\text{1. NaH, THF, } N_2\text{, 0–5 °C}} \mathrm{RCH(OMe)COOH} \qquad (687)$$

3. HCl (pH = 1)

R =	C_5H_{11}	C_6H_{13}	$C_3H_5(CHMe)_2$	Me_2CH	C_3H_7	C_4H_9	C_7H_{15}
% Yield =	54	53	56	59	57	53	54

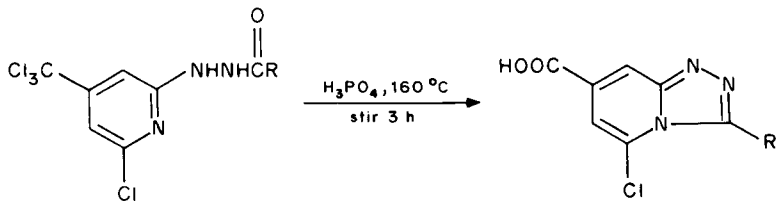
% Yield =	C_8H_{17}	cyclohexyl
	51	63

$$\mathrm{R^1CR^2(=O)} \xrightarrow[\text{TEBA, room temp., 2–3 h}]{\text{1. } CHCl_3\text{, NaOH, } R^3XH} \mathrm{R^1C(R^2)(XR^3)COOH} \qquad (688)$$

TABLE 55. Phase transfer preparation of substituted acetic acids

R^1	R^2	R^3	X	Reference
Me	Me	Me	O	1571
Me	Ph	H	O	1570
Me	Ph	Me	O	1571
Et	Ph	H	O	1570
Me	*i*-Bu	Et	O	1571
i-Bu	OBu-*i*	Me	O	1571
Me	Me	*c*-Hex	S	1571
Ph	Ph	H	O	1570
$PhCH_2$	$PhCH_2$	H	O	1570
Me	Et	*i*-Bu	O	1571
Cyclohexane		*i*-Bu	O	1571
Et	C_5H_{11}	*i*-Bu	O	1571
Me	Me	Et	O	1571
Me	Me	$C_{12}H_{25}$	O	1571
Cyclohexane		Me	O	1571
Me	C_3H_7	Me	O	1571
Me	Me	Ph	O	1571
Me	Me	Ph	S	1571

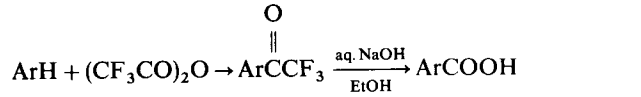
An interesting product is obtained when the trichloromethyl group of 4-trichloromethyl-6-chloro-2-pyridylhydrazides is subjected[1572] to hydrolysis using polyphosphoric acid. Not only is a carboxylic acid function formed from the trichloromethyl group, but a cyclization also occurs (equation 689) to produce substituted antiallergenic 5-chloro-s-triazolo[4,3-*a*]pyridine-7-carboxylic acids.



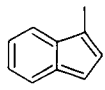
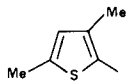
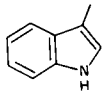
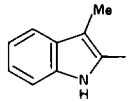
(689)

R = H, chloroalkyl, Ph, halophenyl, alkylphenyl

When reactive aromatic and heterocyclic molecules are treated[1573] with trifluoroacetic anhydride, α,α,α-trifluoroacetophenones are obtained, which upon treatment with aqueous sodium hydroxide in ethanol are hydrolyzed (equation 690) to the corresponding aromatic or heterocyclic carboxylic acids. Although not a true trihalide hydrolysis, since the resulting acids contain one carbon atom less than the acetophenone starting material, this trihalide hydrolysis-elimination does produce carboxylic acids in good yields.



(690)

Ar	Yield (%)
p-$Me_2NC_6H_4$	75
p-$Et_2NC_6H_4$	72
2,4,6-$(MeO)_3C_6H_2$	0
	Not reported
	92
	96
	78
	0

*6. *Hydrolysis of dihalides*

A variety of reagents have been used to catalyze the conversion of 1,1-dihalovinyl groups to carboxylic acids. For example, 1,1-dibromovinyl groups have been converted[1574] to the corresponding carboxylic acid in the presence of palladium [1,2-

bis(diphenylphosphino)ethane][Pd(diphos)] (equation 691 and Table 56).

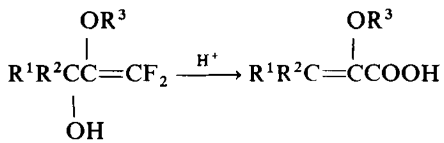
$$R^1R^2C{=}CBr_2 \xrightarrow[\text{Pd(diphos), PEG-400, 60–65 °C, 17 h}]{\text{NaOH or KOH, } N_2} R^1R^2CHCOOH \quad (691)$$

TABLE 56. Conversion of 1,1-dibromovinyl groups to carboxylic acids

R^1	R^2	Base	Yield(%)
Ph	H	NaOH	95
o-Tol	H	NaOH	51
p-Tol	H	NaOH	77
p-ClC_6H_4	H	NaOH	35
p-ClC_6H_4	H	KOH	56
p-An	H	NaOH	85
PhCH=CH	H	NaOH	58
Ph	Me	NaOH	18
Ph	Me	KOH	23
—$(CH_2)_2CHMe(CH_2)_2$—		NaOH	42

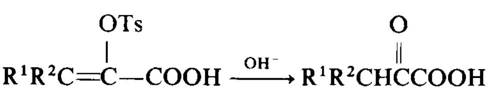
With *gem*-difluoroolefins, reagents ranging from sulfuric acid to mercuric acetate in trifluoroacetic acid have been used[1575] (equation 692 and Table 57) to produce carboxylic acids. However, if the *gem*-difluoroolefin contains a β-alkoxy group and γ-hydroxy group, the products which result[1576] from acid hydrolysis are α,β-unsaturated carboxylic acids (equation 693). If the R^3 group is tosylate, then addition treatment with base produces α-ketoacids[1576] (equation 694).

$$R^1R^2C{=}O \xrightarrow{Ph_3P{=}CF_2} R^1R^2C{=}CF_2 \xrightarrow[\text{D}]{\text{A,B,C or}} R^1R^2CHCOOH(R^3) \quad (692)$$



(693)

R^1 = Me, Ph; R^2 = Me, H; R^3 = Ph, Ph



(694)

R^1 = Me, Ph; R^2 = Me, H

Replacement of one of the halides of the 1,1-dihalovinyl group with a phenylthio function does not change the course of the reaction, since upon treatment with mercuric acetate in formic acid the 1-chloroalk-1-enyl phenyl sulfides are converted[1577] into carboxylic acids (equation 695).

TABLE 57. Conversion of 1,1-difluorovinyl groups to carboxylic acids and esters

Olefin	Method[a]	Product	Yield (%)
$PhCH{=}CF_2$	A	$PhCH_2COOH$	93
$PhCH{=}CF_2$	B	$PhCH_2COOMe$	80
$p\text{-}Me_2CHC_6H_4CH{=}CF_2$	A	$p\text{-}Me_2CHC_6H_4CH_2COOH$	70
$p\text{-}Me_2CHC_6H_4CH{=}CF_2$	B	$p\text{-}Me_2CHC_6H_4CH_2COOMe$	81
$PhCMe{=}CF_2$	A	$PhCHMeCOOH$	94
$p\text{-}Me_2CHCH_2C_6H_4CMe{=}CF_2$	A	$p\text{-}Me_2CHCH_2C_6H_4CHMeCOOH$	80
$n\text{-}C_6H_{13}CH{=}CF_2$	C	$n\text{-}C_7H_{15}COOH$	69
$n\text{-}C_{10}H_{21}CH{=}CF_2$	C	$n\text{-}C_{11}H_{23}COOH$	88
$n\text{-}C_{10}H_{21}CH{=}CF_2$	D	$n\text{-}C_{11}H_{23}COOEt$	40[b]

[a]Method: A, conc. H_2SO_4, $-10\,^\circ C$, stir room temp. 3 h; B, conc. $H_2SO_4 + R^3OH$; C, $Hg(OAc)_2$, CF_3COOH, then aqueous $NaHCO_3$ and H_2S; D, $Hg(OAc)_2$, CF_3COOH, THF, then R^3OH.
[b]Determined by GLC.

$$RCH_2CH_2SPh \xrightarrow[C_5H_5N]{SO_2Cl_2,CCl_4} RCH{=}\overset{\displaystyle Cl}{\overset{|}{C}}SPh \xrightarrow[\substack{HCO_2H\\ 50\,^\circ C,3\,h}]{Hg(OAc)_2} RCH_2COOH \tag{695}$$

R =	C_6H_{13}	C_5H_{11}	*n*-Pr	*i*-Pr	Ph
% Yield (olefin) =	74	70	69	72	86
% Yield (acid) =	71	62	—	—	26

One direct method reported[1578] for the preparation of tertiary alkylacetic acids involves the condensation of 1,1-dichloroethene with a reagent (olefin, alcohol or alkyl halide), which will readily form a carbocation in concentrated sulfuric acid. The intermediate 1,1-dichloride products from this condensation are not isolated but are hydrolyzed immediately *in situ* to produce the tertiary alkylacetic acids (equation 696).

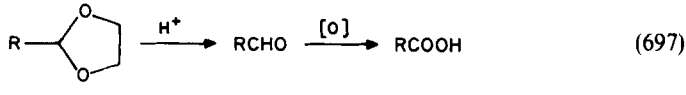
$$\begin{array}{c} R^1 \\ | \\ MeCX \\ | \\ R^2 \end{array} + H_2C{=}CCl_2 \xrightarrow[2.\ H_2O]{1.\ H_2SO_4} \begin{array}{c} R^1 \\ | \\ MeCCH_2COOH \\ | \\ R^2 \end{array} \tag{696}$$

R^1	R^2	X	Total Rx time (h)	Temp. (°C)	Yield (%)
Me	Me	OH	2.5[a]	2	90
Me	Me	Cl	4[a]	6	77
Me	Me	OMe	2.5[a]	5	55
Me	Et	OH	3[a]	6	53
Me	Et	OH	3[b]	4–11	72
Me	Et	OH	4.5[b]	2–11	75
Et	Et	OH	3.5[a]	4	13
Et	Et	OH	5[b]	4–17	30

[a]Using 99% sulfuric acid by weight.
[b]Using 96–98% sulfuric acid by weight.

*7. *Miscellaneous dealkylation reactions of esters*

Since conversion of dioxolanes into carboxylic acids usually involves treatment with acid first followed by oxidation (equation 697) to remove the protecting group, a study of nonacidic alternatives for the conversion of dioxolanes into carboxylic acids was undertaken[1579] to permit the introduction of an acid group into molecules which contain various acid-sensitive functionalities. The alternative found most useful was to convert the cyclic acetals into their corresponding bromo esters using *N*-bromosuccinimide followed by Zn induced 1,2-elimination (equation 698). Studies[1579] of the conditions which would afford the best conversion of the dioxolanes (R = Ph) to the corresponding acid, established that no reaction was observed when the intermediate 2-bromoethyl benzoate was treated with zinc in refluxing tetrahydrofuran, zinc activated with copper sulfate, ultraactive zinc prepared by reaction of zinc with potassium metal or prepared by sodium naphthalide reduction of zinc chloride, while some modest conversion was observed by utilizing zinc in refluxing methyl or ethyl alcohol (42–46% conversion) or zinc in refluxing aqueous tetrahydrofuran (44% conversion). By far the best conditions discovered for this conversion involved the treatment of 2-bromoethyl benzoate with zinc in refluxing aqueous tetrahydrofuran containing sodium iodide, which afforded an 86% yield of benzoic acid (99% if the yield was based upon recovered starting material). Other dioxolanes converted into carboxylic acids using this approach are reported in Table 58.



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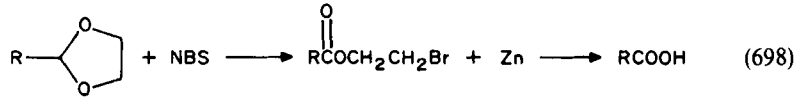
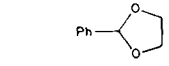
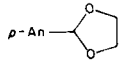
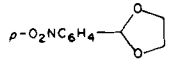
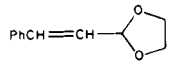
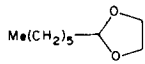
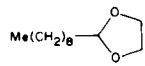


(698)

TABLE 58. Preparation of acids by reactions of dioxolanes with zinc

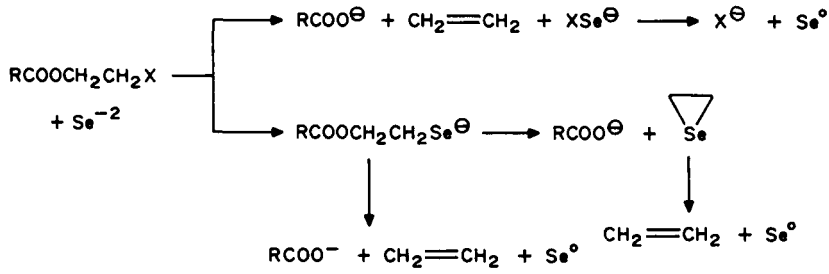
Acetal	Reaction conditions	Acid	Yield (%)
	Zn + NaI, 50% THF reflux 24 h	PhCOOH	99
	Zn + NaI, 50% THF reflux 24 h	*p*-AnCOOH	96
	Zn + $ZnCl_2$, Me_2SO reflux	*p*-$O_2NC_6H_4COOH$	58
 *trans*	Zn + $ZnCl_2$, Me_2SO reflux	PhCH=CHCOOH *trans*	91
	Zn + $ZnCl_2$, Me_2SO reflux	$Me(CH_2)_5COOH$	91
	Zn + $ZnCl_2$, Me_2SO reflux	$Me(CH_2)_8COOH$	76

Other reagents which have been used to cleave bromoethyl esters to give carboxylic acids include thiocarbonate[1580], which affords acids in 75–86% yields, cobalt(I) phthalocyanine[1581] which was used to cleave both bromoethyl and chloroethyl esters to acids, and sodium hydrogen selenide[1582] (equation 699). In the case of the latter reagent the author postulates[1582] that the reaction mechanism may involve one or more of three different pathways illustrated below, all of which are kinetically indistinguishable.

$$RCOOCH_2CH_2X + NaHSe \xrightarrow[\text{2. reflux 5 min}]{\text{1. EtOH, room temp. 1 h}} RCOOH \qquad (699)$$
$$\text{3. HCl}$$

$X = Cl, Br$

R	X	Acid	Yield (%)
Ph	Br	PhCOOH	99
Ph	Cl	PhCOOH	95
p-An	Br	*p*-AnCOOH	96
p-ClC_6H_4	Br	*p*-ClC_6H_4COOH	92
n-$C_{11}H_{23}$	Br	*n*-$C_{11}H_{23}COOH$	93



Another novel nonacidic method for dealkylation of esters involves the conversion of the ester into a trimethylsilyl ester which is then hydrolyzed to the free acid[1583,1584]. Two approaches have been used to produce the trimethylsilyl esters. The first, which was used for *t*-butyl esters exclusively, involved reduction with trimethylsilyl triflate[1583] (equation 700), while the second utilized trimethylsilyl chloride in the presence of sodium iodide[1584] (equation 701) and was found to be effective for a variety of esters including *t*-butyl esters, although the yields of the trimethylsilyl esters decreased with increasing bulkiness of the nonester alkyl group.

$$RCOOBu\text{-}t + F_3CSO_2OSiMe_3 \xrightarrow[\text{Ar, reflux 1 h}]{Et_3N, \text{dioxane}} \left[RC(\overset{\oplus}{O}\text{-}SiMe_3)(\overset{\oplus}{O}\cdot Bu\text{-}t) + CF_3SO_3^{\ominus} \right]$$

$$\xrightarrow[-(CF_3SO_3H)]{-(CH_2=CMe_2)} RCOOSiMe_3 \xrightarrow{H_2O} RCOOH \qquad (700)$$

R	Reaction time (min)	% Yield ester	% Yield acid
n-C_5H_{11}	20	82	—
$MeOOCCH_2$	20	87	—
$PhCH_2OOCCH_2CH_2$	3	79	—
$PhCH_2OOCNHCH_2$	10	87	—
$PhCH_2CH(NHCOOCH_2Ph)$	30	—	78
p-$Me_2NC_6H_4$	5	>90	—
p-An	30	—	98
Ph	60	82	—
p-ClC_6H_4	60	—	89
p-$O_2NC_6H_4$	240	—	88

$$R^1COOR^2 + Me_3SiCl \xrightarrow[\text{stir}]{\text{NaI, MeCN}} R^1COOSiMe_3 \xrightarrow{H_2O,\text{ room temp.}} R^1COOH \qquad (701)$$

R^1	R^2	Temp. (°C)	Time (h)	% Yield ester
Me	Me	70–75	5	86
Me	Et	70–75	20	62
Me	i-Pr	70–75	35	37
Me	t-Bu	45	0.2	100
Me	$PhCH_2$	45	0.5	92
i-Pr	Me	70–75	9	79
$Me(CH_2)_4$	Me	70–75	7	82
c-Hex	Me	70–75	9	86

Oxidative cleavage of esters has also been reported[1585–1587] to be an effective approach to the preparation of carboxylic acids. Selective oxidative cleavage of benzylic esters with nitrosonium hexafluorophosphate[1585] (equation 702) creates a cationic center which

$$R^1COOCHR^2Ph + NOPF_6 \xrightarrow[\substack{50\,^\circ C,\,0.5\,h\\ -HNO}]{MeNO_2,\,N_2,\,\text{stir}} R^1COO\overset{+}{C}R^2Ph \xrightarrow{-(PhCOR^2)} R^1CO^+ \xrightarrow{H_2O} R^1COOH + HX \qquad (702)$$

Ester	Acid	Yield (%)
Benzyl benzoate	Benzoic	85
Benzyl cyclohexanecarboxylate	Cyclohexanecarboxylic	93
Benzyl undecanoate	Undecanoic	80
Benzhydryl benzoate	Benzoic	97
Benzhydryl p-chlorobenzoate	p-Chlorobenzoic	98
Benzhydryl p-anisate	p-Anisic	82
Benzhydryl cyclohexanecarboxylate	Cyclohexanecarboxylic	95

induces spontaneous fragmentation into an acylium ion and a carbonyl compound which, upon subsequent quenching of the acylium ion with water, produces the carboxylic acid. Esters have also been oxidatively cleaved by using superoxides (equation 703), and it has been reported[1586] that sodium superoxide in dimethyl sulfoxide cleaves esters more rapidly than potassium superoxide in benzene containing 18-crown-6 ether.

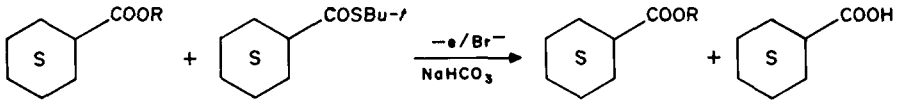
$$R^1COOR^2 \xrightarrow[\text{room temp.}]{NaO_2, Me_2SO} R^1COOH \qquad (703)$$

Ester	Rx time	Acid	Yield (%)
p-NCC_6H_4COOEt	5 min	*p*-$H_2NCOC_6H_4COOH$	96
p-$MeOOCC_6H_4COOMe$	15 min	*p*-$HOOCC_6H_4COOH$	97
n-$C_{11}H_{23}COOMe$	3 h	*n*-$C_{11}H_{23}COOH$	91
n-$C_{13}H_{27}COOMe$	8 h	*n*-$C_{13}H_{27}COOH$	85

Oxidative dealkylation of *t*-butyl thioate esters has been accomplished[1587] under neutral conditions by electrooxidation using halide salts as electrolytes and platinum electrodes at room temperature (equation 704). For this reaction the *t*-butyl esters are better than either the ethyl or the phenyl analogs because they have a greater resistance toward hydrolysis under both basic and acidic conditions. Other electrolytes, including KF, LiI, $LiNO_3$ and $(n\text{-}Bu)_4NClO_4$, have also been used in the reaction. The above electrooxidation reaction has also been performed on cyclohexane *t*-butyl thioate in the presence of other compounds to examine the stability of other functional groups during the dealkylation of the *t*-butyl group. Stability was observed for *t*-alcohols, ketones, esters (equation 705) and α,β-unsaturated ketones or esters, but not observed for functional groups which are susceptable to oxidation such as primary or secondary alcohols, aldehydes, nonconjugated olefins or amines.

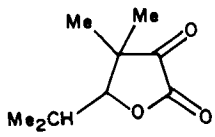
$$RCOSBu\text{-}t \xrightarrow[\substack{0.2A,\ \text{room temp.}\\ \sim 2\,h}]{MeCN,\ H_2O,\ \text{electrolyte}} RCOOH \qquad (704)$$

R	Electrolyte	Yield (%)
c-Hex	LiBr	87
c-Hex	$(n\text{-}Bu)_4NBr$	94
$Me(CH_2)_4$	LiCl	83
$Me(CH_2)_4$	LiBr	96
Ph	$(n\text{-}Bu)_4NBr$	94



R=Ph_3C, *p*-$MeOC_6H_4CH_2$ (705)

Basic hydrolysis of alkyl-substituted dihydrofurandiones has been reported[1588] to afford good to excellent yields of α-oxocarboxylic acids (equation 706).

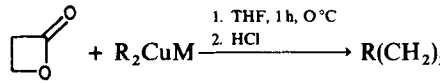


(706)

Organometallic reagents have also been found to be useful for the preparation of carboxylic acids from specific esters. For example, good yields of carboxylic acids may be obtained[1589] from the corresponding allyl esters (equation 707) by treatment with lithium dimethyl cuprate at 0 °C for one hour. This selective removal of allyl groups from esters is accomplished under reaction conditions that are not strongly basic and thus this approach to acid preparation from esters should find use in situations where neutral reagents would fail to discriminate between various types of esters. Organocuprates have also been used[1590] in the regiospecific ring opening of β-propiolactones (equation 708) to produce a three-carbon homologated carboxylic acid (Table 59).

$$\mathrm{RCOOCH_2CH{=}CH_2} \rightarrow \mathrm{RCOOLi} + \mathrm{MeCu} + \mathrm{CH_2{=}CHCH_2Me}$$
$$\downarrow \mathrm{H_3O^+}$$
$$\mathrm{RCOOH} \qquad (707)$$

R =	Ph	*p*-ClC_6H_4	*p*-$MeOOCC_6H_4$	*n*-$C_{11}H_{23}$	*n*-$C_8H_{17}CH{=}CH(CH_2)_7$(*cis*)
% Yield =	85	78	75	81	80



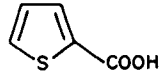
(708)

Mercuric acetate is another organometallic reagent which has found use[1591] in the preparation of carboxylic acids by the cleavage of specific esters, as in this case of cinnamyl esters. This mild cleavage occurs under neutral conditions and involves a mercuration demercuration mechanism (equation 709).

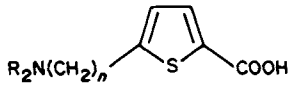
$$\mathrm{RCOOCH_2CH{=}CHPh} \xrightarrow[\text{2. } Na_2CO_3 \text{ or } K_2CO_3]{\text{1. } Hg(OAc)_2, HNO_3, MeOH,\ 20°C, 2\text{–}4\,h} \mathrm{RCOOCH_2CH(HgX)CH(OMe)Ph}$$
$$\downarrow \mathrm{KSCN}, H_2O, \text{ cyclohexane}, 23\,°C, 12\text{–}16\,h \qquad (709)$$
$$\mathrm{RCOOH + CH_2{=}CHCH(OMe)Ph}$$

R = *c*-Hex, Ph, *p*-An, $C_6H_5CH_2$

Solvated electron reduction of 2-thiophenecarboxylic acid causes ring opening to produce[1592] 5-mercapto-3(*Z*)-alkenoic acids (equation 710), while similar treatment of 5-dialkylaminoalkyl-2-thiophenecarboxylic acids, because of the specific influence of the substituted amino group which is removed from the thiophene ring by one or two carbon atoms, causes[1593] elimination of the sulfur atom (equation 711) to give dialkylamino-*S*-

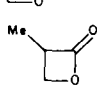
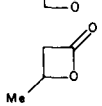
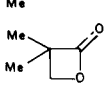
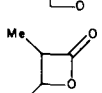
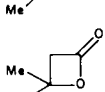
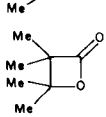


$\xrightarrow{\bullet}$ $\mathrm{HSCH_2CH{=}CHCH_2COOH}$ (*Z*) (710)



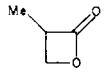
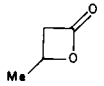
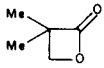
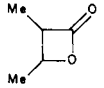
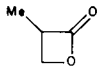
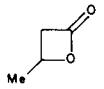
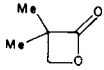
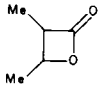
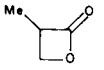
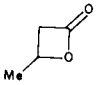
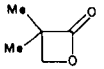
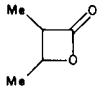
$\xrightarrow{\bullet}$ $\mathrm{R_2N(CH_2)_nCH{=}CH{-}CH{=}CHCOOH}$ (*E*) (*E*) (711)

TABLE 59. Preparation of acids by reaction of β-propiolactones with organocuprates R_2CuM

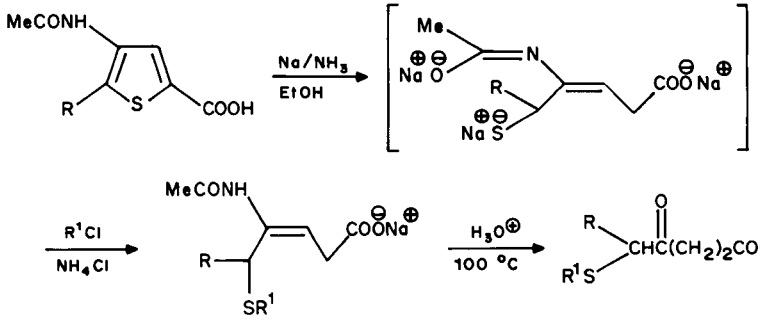
R	M	Lactone	Product	Yield (%)
Me	Li		$Me(CH_2)_2COOH$	70
Me	MgBr		$Me(CH_2)_2COOH$	86
n-Bu	Li		$Me(CH_2)_5COOH$	83
n-Bu	MgBr		$Me(CH_2)_5COOH$	92
i-Pr	MgBr		$Me_2CH(CH_2)_2COOH$	79
t-Bu	MgCl		$Me_3C(CH_2)_2COOH$	88
$CH_2{=}CHCH_2$	MgBr		$CH_2{=}CH(CH_2)_3COOH$	65
$CH_2{=}CH$	MgBr		$CH_2{=}CH(CH_2)_2COOH$	87
Ph	Li		$Ph(CH_2)_2COOH$	20
Ph	MgBr		$Ph(CH_2)_2COOH$	80
n-Bu	MgBr		$Me(CH_2)_4CHMeCOOH$	85
n-Bu	MgBr		$Me(CH_2)_3CHMeCH_2COOH$	89
n-Bu	MgBr		$Me(CH_2)_4CMe_2COOH$	82
n-Bu	MgBr		$Me(CH_2)_3(CHMe)_2COOH$	82
n-Bu	MgBr		$Me(CH_2)_3CMe_2CH_2COOH$	0
n-Bu	MgBr		$Me(CH_2)_3(CMe_2)_2COOH$	0

(*continued*)

TABLE 59 (*continued*)

R	M	Lactone	Product	Yield (%)
Me	MgBr		$MeCH_2CHMeCOOH$	85
Me	MgBr		Me_2CHCH_2COOH	80
Me	MgBr		$MeCH_2CMe_2COOH$	91
Me	MgBr		$Me_2CHCHMeCOOH$	81
$CH_2=CH$	MgBr		$CH_2=CHCH_2CHMeCOOH$	72
$CH_2=CH$	MgBr		$CH_2=CHCHMeCH_2COOH$	27
$CH_2=CH$	MgBr		$CH_2=CHCH_2CMe_2COOH$	48
$CH_2=CH$	MgBr		$CH_2=CH(CHMe)_2COOH$	17
Ph	MgBr		$PhCH_2CHMeCOOH$	52
Ph	MgBr		$PhCHMeCH_2COOH$	11
Ph	MgBr		$PhCH_2CMe_2COOH$	3
Ph	MgBr		PhCHMeCHMeCOOH	6

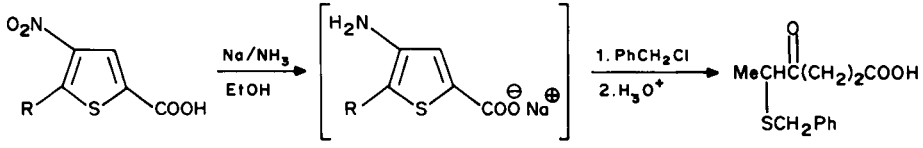
trans-2(*E*),4(*E*)-alkadienoic acids. If the amino group is located on the thiophene ring and not in a side-chain, however, then the mode of ring opening which occurs upon treatment with a solvated electron proceeds in the same way as the opening of the 2-thiophenecarboxylic acids (equation 710). The enamino derivatives obtained[1594] as products from this reaction are readily hydrolyzed in the presence of a free amino group but are more stable in the case of acylamino substituents (equation 712).



(712)

R	R^1	Yield (%)
Me	$2,4\text{-}(O_2N)_2C_6H_3$	45
Me	$PhCH_2$	70
H	$PhCH_2$	53
Et	$PhCH_2$	80

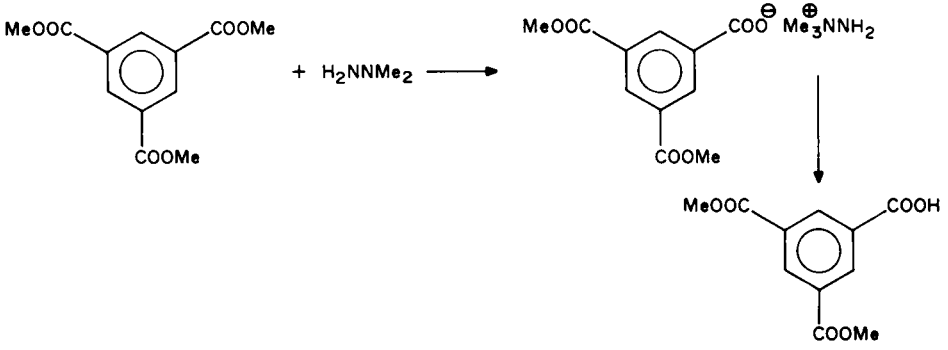
The elements of this reaction have been used[1594] in a two-step synthesis of 5-mercapto-4-ketoalkanoic acids from 3-nitrothiophenecarboxylic acids (equation 713).



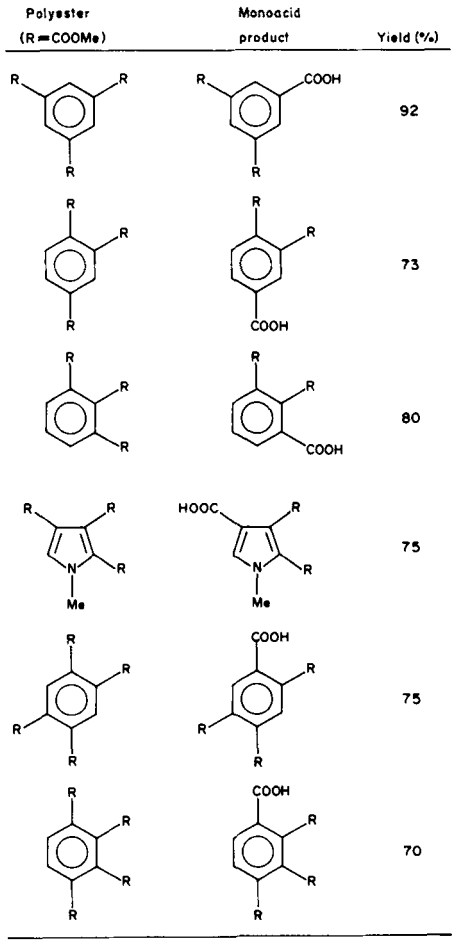
R = Me Et
Yield (%) = 45 67

(713)

On treatment with 1,1-dimethylhydrazine, polymethyl esters undergo selective demethylation at the least hindered site to give monoacid polyesters[1595] (equation 714).



(714)



Finally, it has been reported[1596] that carboxylic acids may also be produced from esters by stereoselective enzymatic hydrolysis, since lipase from *Candida cylindracea* hydrolyzes octyl *R*(+)-2-chloropropionate to *R*(+)-2-chloropropionic acid but does not hydrolyze octyl S(−)-2-chloropropionate. This same enzyme, however, exhibits no stereoselectivity in the hydrolysis of the methyl ester of the same acid, and thus both methyl *R*(+)- and *S*(−)-2-chloropropionate were hydrolyzed to *R*(+)- and *S*(−)-2-chloropropionic acid.

*B. Acids by Condensation Reactions

*2. Doebner reaction

Although the Doebner reaction normally produces α,β-unsaturated acids when pyridine is employed as the reaction solvent, treatment of malonic acid with 2,2-dibromopropanal in the presence of 1% pyridine at 60 °C without solvent affords 4,4-dibromo-3-hydroxypentanoic acid (75%), which then on dehydration gives a quantitative

yield of 4,4-dibromo-2-pentenoic acid (equation 715)[1597].

$$CH_3CBr_2CHO + CH_2(COOH)_2 \xrightarrow{1\%\text{ pyridine}} CH_3CBr_2CH(OH)CH_2COOH$$

$$\xrightarrow[\text{heat}]{(F_3CCO)_2O} CH_3CBr_2CH{=}CHCOOH \qquad (715)$$

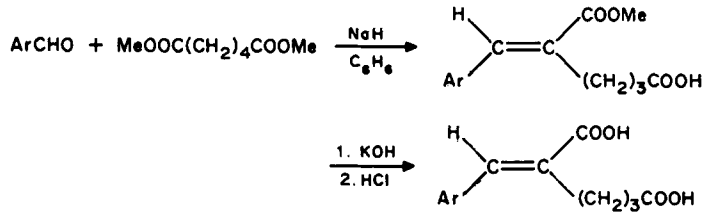
In a related series of reactions, which the authors referred to as Knovenagel condensations, hexanal was allowed to react with malonic acid in the presence of a molecular equivalent of various tertiary amines of different basicity and steric requirements[1598]. The ratio of the resulting α,β- and β,γ-unsaturated octenoic acids (equation 716) was strongly influenced by the nature of the amine catalyst. Thus, amines possessing a basic center with little steric hindrance, such as pyridine, 3- and 4-methylpyridine, effected formation of 2-octenoic acid mainly, while more sterically encumbered amines, such as 2-methylpyridine and 2,6-dimethylpyridine, lead to predominant formation of 3-octenoic acid.

$$CH_3(CH_2)_4CHO + CH_2(COOH)_2 \xrightarrow[90\,^\circ C,\,10\,h]{3^\circ\text{ amine}} \underset{(\alpha,\beta)}{CH_3(CH_2)_4CH{=}CHCOOH}$$

$$+ \underset{(\beta,\gamma)}{CH_3(CH_2)_3CH{=}CHCH_2COOH} \qquad (716)$$

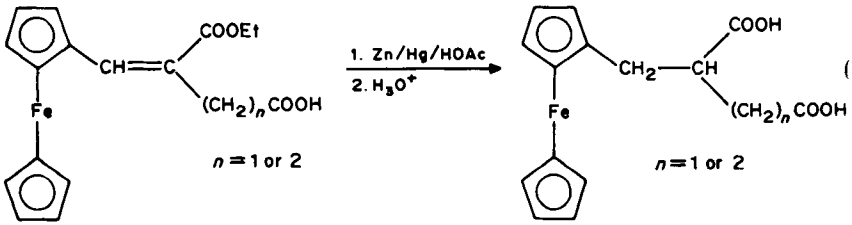
3. Stobbe condensation

Stobbe condensation of aryl aldehydes including benzaldehyde, substituted benzaldehydes, furan-2-carboxaldehyde and 1-naphthaldehyde, with dimethyl adipate in the presence of sodium hydride has been reported to yield the expected half esters, which were then saponified to give the corresponding unsaturated dicarboxylic acids (equation 717)[1599].



(717)

Ferrocenecarboxaldehyde reacts with ethyl succinate and ethyl glutarate to afford the expected half esters, which can be reduced under the conditions of Clemmensen reduction (catalytic reduction failed) and finally hydrolyzed to the respective dibasic acids (equation 718)[1600].

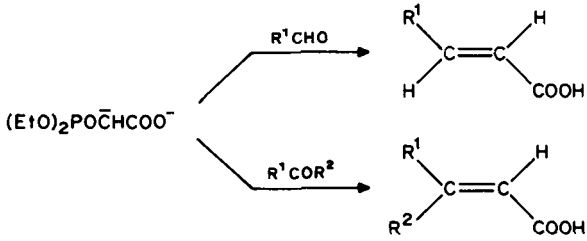


(718)

*5. *Wittig-type reactions*

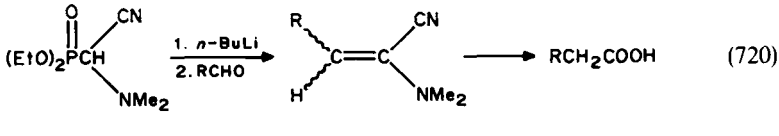
The Wittig-type reactions discussed in this section are limited to examples in which free carboxylic acids are either formed directly or are the major end products of the synthetic scheme. Similar olefination reactions leading to esters and other carboxylic acid derivatives are discussed earlier and in subsequent sections.

The procedure for the synthesis of α,β-unsaturated acids using the dianion of dibenzyl carboxymethanephosphonate (see Section II.B.5, equation 33) has been improved by employing the dilithio salt of diethyl carboxymethanephosphonate as the olefinating agent (equation 719)[1601]. This reagent is cheaper than its dibenzyl counterpart, and diethyl phosphoate is easier to separate from the alkenoic acid than dibenzyl phosphonate. As indicated in equation 719, aromatic and aliphatic aldehydes as well as aliphatic ketones react to give predominately the *E* alkenoic acids.

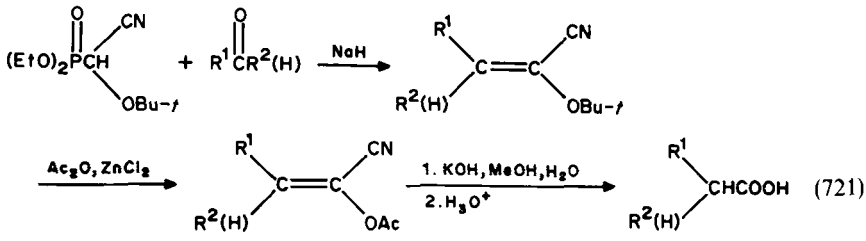


(719)

The synthetic utility of tetraethyl dimethylaminomethylenediphosphonate[132] (see Section II.B.5, equation 34) has been further developed to include the preparation of α,β-unsaturated acids derived from this reagent and thiophene- and benzothiophene-2-carboxyaldehydes, benzofuran-2-carboxaldehyde, and a series of aliphatic aldehydes[1602]. In a related procedure, which also involves initial formation of enamine intermediates, the lithium salt of 1-dimethylamino-1-cyanomethanephosphonic acid diethyl ester reacts with various aliphatic and aromatic aldehydes, as well as acetophenone, to give cyanoenamines, hydrolysis of which affords the homologous carboxylic acids (equation 720)[1603]. Similarly, diethyl *tert*-butoxy (cyano) methylphosphonate reacts with aldehydes and ketones to produce α-*tert*-butoxyacrylonitriles, which were converted to the less hindered α-acetoxy derivatives. These in turn can be hydrolyzed to the respective carboxylic acids (equation 721)[1604]. If sodium alkoxides or amines are substituted for methanolic potassium hydroxide in reactions with the α-acetoxyacrylonitriles, then carboxylic esters and amides, respectively, are obtained.

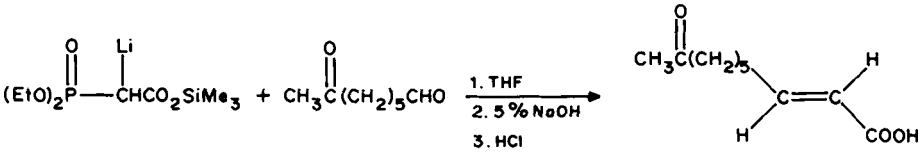


(720)



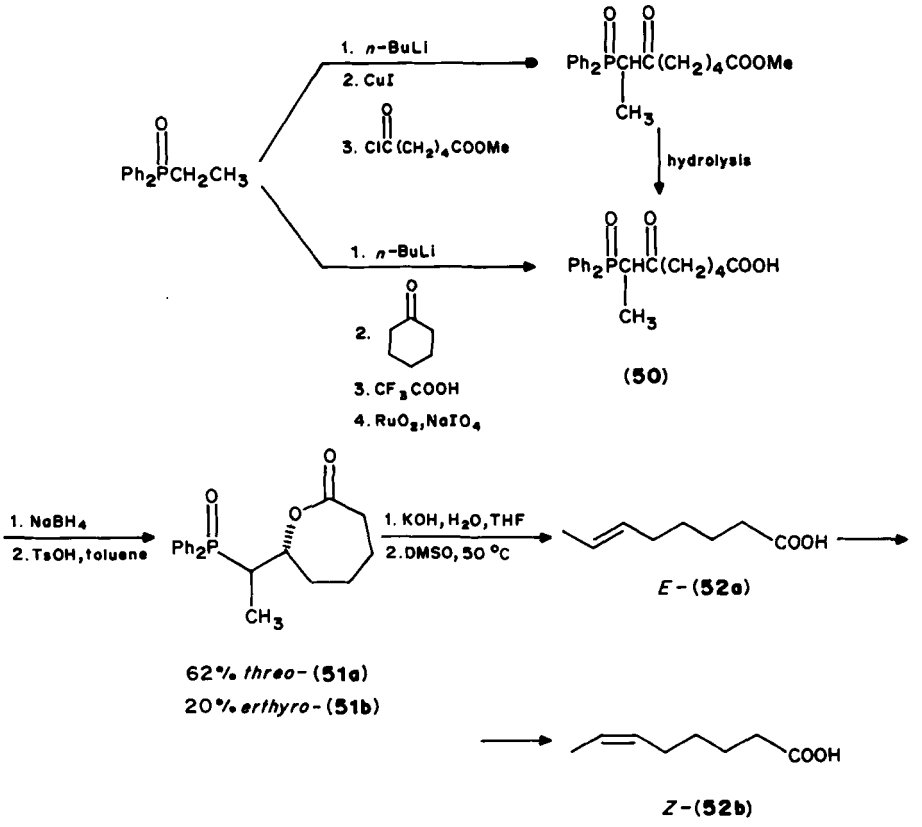
(721)

As mentioned previously, reactions utilizing alkoxycarbonyl-stabilized phosphonate esters require acidic or alkaline hydrolysis of the resulting carboxylic esters to give free acids. However, the lithium salt of diethyl trimethylsilyloxycarbonylmethanephosphonate serves as a convenient acid precursor by virtue of the fact that the trimethylsilyl ester function undergoes facile hydrolysis simply by quenching the reaction mixture with 5% aqueous sodium hydroxide[1605]. This procedure is exemplified by the synthesis of (*E*)-9-oxo-2-decenoic acid (Queen Substance) in 70% yield (equation 722)[1605].



(722)

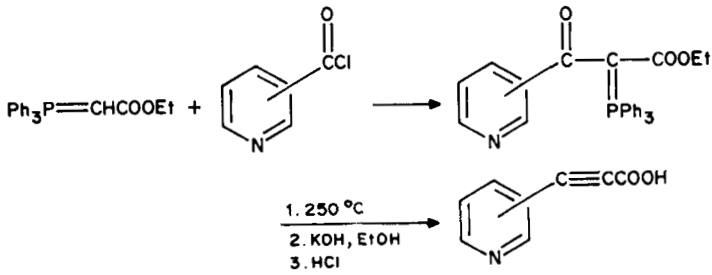
Lithium and copper(I) salts of phosphine oxide α-anions can be used in a general synthesis of unsaturated acids as illustrated in Scheme 8 for the preparation of the (*E*) and (*Z*) isomers of 5-octenoic acid[1606].



SCHEME 8

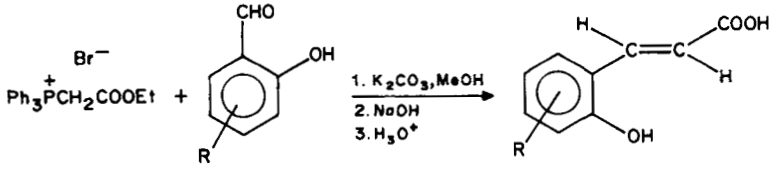
The common intermediate, Ph_2PO-ketoacid **50** is converted to a mixture of *threo* (**51a**) and *erythro* (**51b**) lactones, which are separated, hydrolyzed, and decomposed thermally to afford the (*E*) (**52a**) and (*Z*) (**52b**) isomers.

A series of pyridylpropiolic acids has been prepared by acylation of ethyl (triphenylphosphoranediyl) acetate with pyridinylcarbonyl chlorides, followed by pyrolysis of the resulting acyl phosphoranes and hydrolysis to form the free acids (equation 723)[1607].



(723)

ortho-Hydroxycinnamic acids can be synthesized in good yields by reaction of (carbethoxymethyl)triphenylphosphonium bromide with *ortho*-hydroxyaromatic aldehydes in a liquid–solid two-phase system consisting of methanol and potassium carbonate (equation 724)[1608].



(724)

7. Malonic ester synthesis

Traditional applications of malonic ester syntheses continue to appear frequently in the literature, and a comprehensive listing of such reactions is beyond the scope of this review. The following examples represent some recent, new applications of this methodology to the preparation of carboxylic acids.

The synthesis of 1,21-heneicosanedioic acid (equation 725) illustrates a novel approach to uneven-number dibasic acids, in which malonic ester serves as a source of one carbon atom rather than two, as it usually does in carboxylic acid synthesis[1609].

$$\mathrm{EtOOC(CH_2)_{10}Br + CH_2(COOEt)_2 \longrightarrow [EtOOC(CH_2)_{10}]_2C(COOEt)_2}$$

$$\xrightarrow[\text{3. 160 °C}]{\text{1. NaOH}\atop\text{2. HCl}\atop\text{4. } CH_3OH,\ HCl} \mathrm{[MeOOC(CH_2)_{10}]_2CHCOOH} \xrightarrow[\text{3. Zn, HOAc}]{\text{1. } Ag_2O\atop\text{2. } Br_2\atop\text{4. hydrolysis}} \mathrm{HOOC(CH_2)_{21}COOH} \quad (725)$$

A convenient and inexpensive method for the synthesis of β-keto acids and methyl ketones takes advantage of the fact that bis(trimethylsilyl) malonate can be acylated with acid chlorides, acyl carbonates and acylimidazoles (RCOX) in the presence of lithium bromide or magnesium chloride and triethylamine (equation 726)[1610]. This route offers a

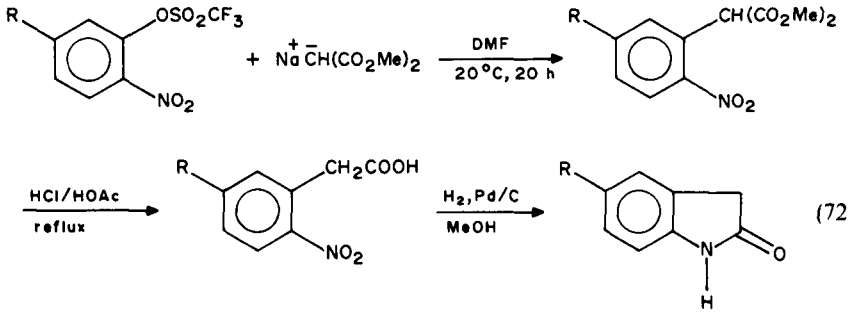
number of advantages over analogous procedures using alkylithium reagents[1611].

$$CH_2(COOSiMe_3)_2 \xrightarrow[2.\ RCOX\ \ 3.\ H_3O^+]{1.\ MX,\ Et_3N} RCOCH_2COOH \text{ or } RCOCH_3 \qquad (726)$$

$MX = LiBr$ or $MgCl_2$

X=Cl, CO_2Et or 

Nitroarylacetic acids can be prepared by alkylating dimethyl sodiomalonate with activated aryl triflates followed by acidic hydrolysis and decarboxylation (equation 727)[1612]. A single *ortho* or *para* nitro group is sufficient to activate the triflate function for displacement by malonate anion. Aryl triflates containing an *ortho* nitro substituent serve as useful oxindole precursors as shown in equation 727. *N*-alkyl- and *N*-arylpyridinium cations can also serve to alkylate and arylate malonate, cyanoacetate and acetoacetate carbanions by transfer of their *N*-substituents[1613].



(727)

2-(Methylthio)alkanoic acids are easily prepared from the carbanions of alkyl- or aryl-substituted malonic esters by successive treatment with *S*-methyl methanethiosulfonate, followed by concurrent alkaline hydrolysis and decarboxylation (equation 728). 2-(Phenylthio)alkanoic acids are available in a similar manner using *S*-phenyl methanethiosulfonate[1614].

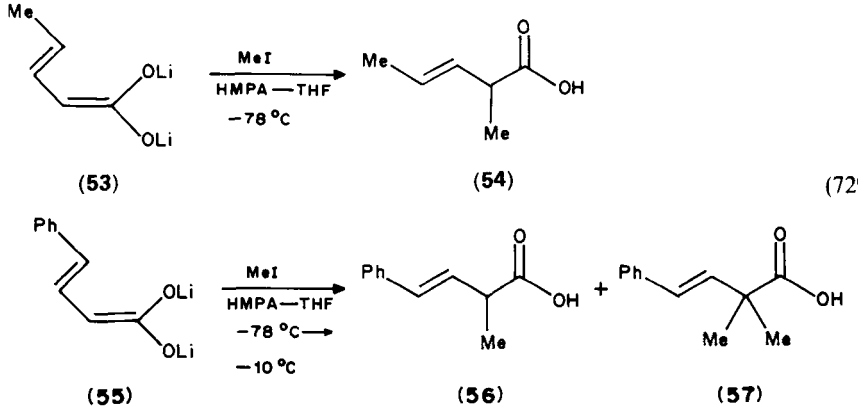
$$R\bar{C}(COOEt)_2 + MeSSO_2Me \longrightarrow \underset{SMe}{RC(COOEt)_2} \longrightarrow \underset{SMe}{RCHCOOH} \qquad (728)$$

**8. From dianions (α-anions) of carboxylic acids*

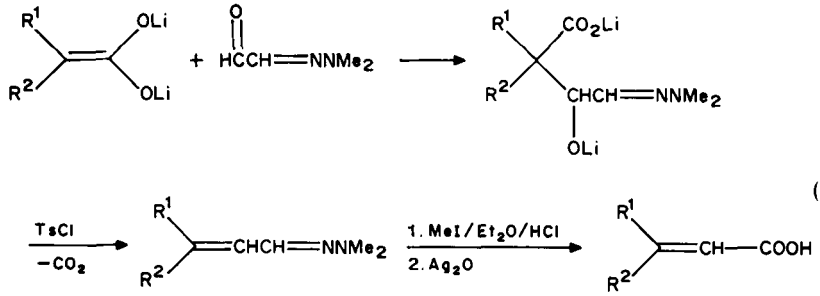
A comprehensive review[1615] of the chemistry of carboxylic acid dianions and ester enolates appeared in 1982, with literature references through 1981. Consequently, this section and Section III.B.4, dealing with α-anions of esters as synthetic intermediates, are limited to synthetic applications of carboxylic acid dianions and ester enolates reported during the period 1982 through 1987.

A study of the alkylation of dilithium salts of several β,γ-unsaturated acids with methyl iodide in HMPA-tetrahydrofuran revealed that methylation occurs regioselectively at the α-position to give mixtures of α-methyl- and α,α-dimethyl products. The ratio of mono- to

dialkylation is dependent upon the structure of the precursor acid and the temperature at which alkylation is carried out[1616]. For example, the dilithio salt of (*E*)-3-pentenoic acid (**53**) affords only (*E*)-2-methyl-3-pentenoic acid (**54**) at −78 °C (equation 729). Methylation of dilithiostyrylacetic acid (**55**) under the same conditions produces a 50:22 percent ratio of (*E*)-2-methyl-4-phenyl-3-butenoic acid (**56**) and (*E*)-2,2-dimethyl-4-phenyl-3-butenoic acid (**57**) (equation 729). When the reaction temperature was raised to −10 °C the yield of monomethylated product **56** increased to 85%. Similar methylation of (*E*)-3-methyl-4-phenyl-3-butenoic acid, (1,2-dihydro-3-naphthyl)acetic acid and 2-indenylacetic acid afforded only α-monomethylated products at −78 °C, although 2-indenylacetic acid underwent predominantly γ-methylation at −5 °C. Methylation of the α-anions of methyl esters corresponding to the acids mentioned above provided somewhat higher ratios of mono- to dimethylated derivatives and exhibited a similar temperature dependence.

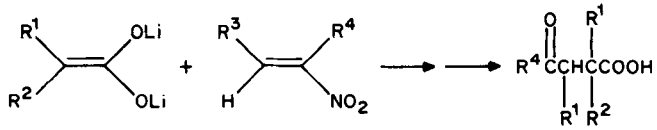


Synthesis of α,β-unsaturated acids by, in effect, inserting a methine group between the α-carbon and the carboxylate function of an appropriate saturated acid can be accomplished by reacting dilithium salts of carboxylic acids with glyoxal (mono)dimethylhydrazone. Reaction of the resulting dilithium salts of β-hydroxy acids with tosyl chloride affords the corresponding α,β-unsaturated aldehyde hydrazones, which are hydrolyzed and oxidized to afford unsaturated acids (equation 730)[1617].



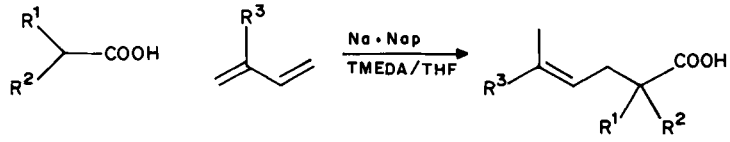
Michael reaction of lithium dianions of carboxylic acids with conjugated nitroolefins at −100 °C followed by treatment of the adducts with aqueous acids affords γ-keto acids in a

one-pot procedure (equation 731)[1618,1619]. Lithium enolates of esters react similarly to give γ-keto esters.



(731)

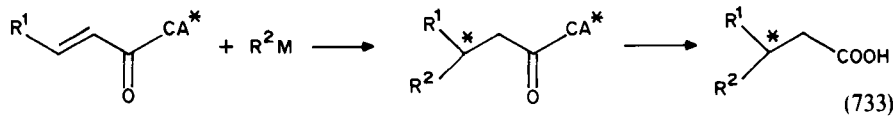
A general method for the synthesis of γ,δ-unsaturated carboxylic acids, which presumably involves α-anion intermediates, is based on the reaction of carboxylic acids with conjugated dienes in the presence of sodium naphthalenide (Na·Nap) and *N,N,N',N'*-tetramethylenediamine (TMEDA) (equation 732)[1620].



(732)

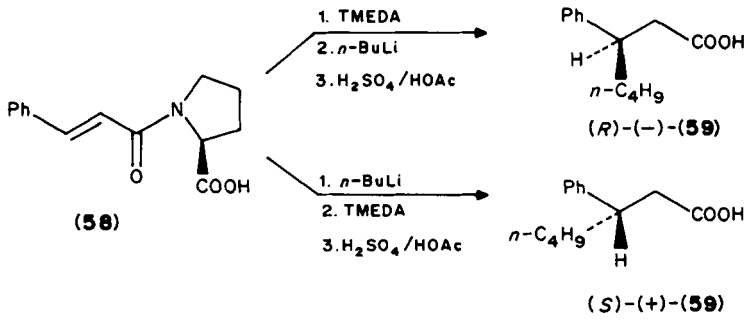
**9. Michael reactions and related conjugate additions*

During the past decade considerable attention has been focused on the synthesis of optically active 3-substituted carboxylic acids and their derivatives by asymmetric conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds[1621]. The fundamental strategy used most often involves reaction of an organometallic addend (R^2M) with an α,β-unsaturated acyl derivative (enoate) in which the acyl carbon is attached to a chiral auxiliary (CA*), which in turn can direct the stereochemistry of the conjugate addition and then be removed to give the desired chiral acid or acid derivative (equation 733).



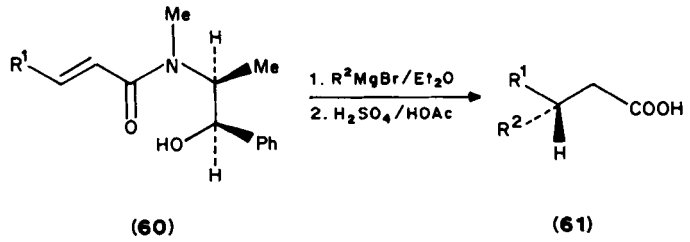
(733)

In a recent study, chiral α,β-unsaturated amido carboxylic acids derived from (*S*)-proline were reacted with organolithium reagents in the presence of tertiary amines to give chiral adducts, which were then hydrolyzed to the respective carboxylic acids. The presence of the tertiary amine increased the chemical yield as well as the optical yield of the reactions, while a change in the order of addition of reactants reversed the configuration of the major isomer. For example, when *n*-butyllithium was added to a mixture of **58** and TMEDA, (*R*)-(−)-3-phenylheptanoic acid (**59**) was obtained in 29% yield and in 51% enantiomeric excess (ee). Addition of TMEDA to a mixture of **58** and *n*-butyllithium gave (*S*)-(+)-**59** in 49% yield and in 39% ee (equation 734)[1622]. Asymmetric conjugate addition of Grignard reagents to α,β-unsaturated amides derived from (*S*)-2-(1-hydroxy-1-methylethyl)pyrrolidine or (*S*)-prolinol in the presence of tertiary amines affords 3-substituted carboxylic acids with ee values up to 89%[1623]. α,β-Unsaturated carboxamides derived from 1-ephedrine (**60**) undergo conjugate addition with Grignard reagents to form optically active acids **61** following acidic hydrolysis. The high degree of stereoselectivity is ascribed to approach of the organomagnesium reagents from the sterically less hindered



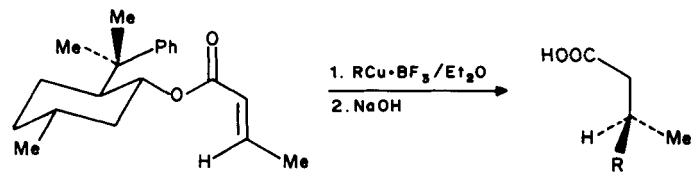
(734)

side of the rigid internal magnesium chelate formed from **60** and an equivalent of Grignard reagent (equation 735)[1624].

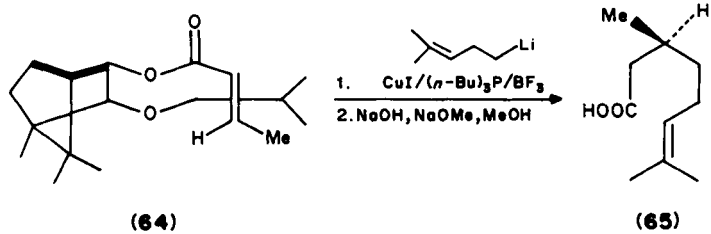


(735)

Chiral auxiliary groups derived from optically active alcohols have proven to be effective for chiral induction in conjugate addition. Thus, BF_3-mediated 1,4-additions of organocopper reagents to α,β-unsaturated ester **62**, prepared from *trans*-crotonic acid and (−)-8-phenylmenthol, occur preferentially on the side of the α,β-double bond opposite the phenyl ring to afford, after saponification, enantiomerically pure 3-substituted alkanoic acids **63** (equation 736)[1625]. Similar reactions of the *cis*-crotonate analog of **62** led mainly



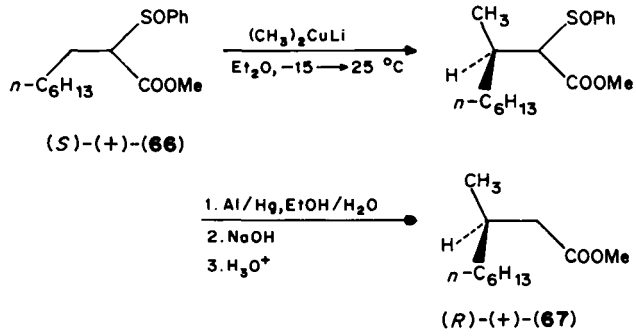
(736)



(737)

to acids with the opposite configuration from 63, but with lower ee values. An enantioselective synthesis of (*S*)-(−)-citronellic acid (**65**) in 92 percent optical purity has been accomplished via addition of 4-methyl-3-pentenylcopper·BF_3·*n*-Bu_3P-complex to chiral crotonate **64** followed by saponification (equation 737)[1626].

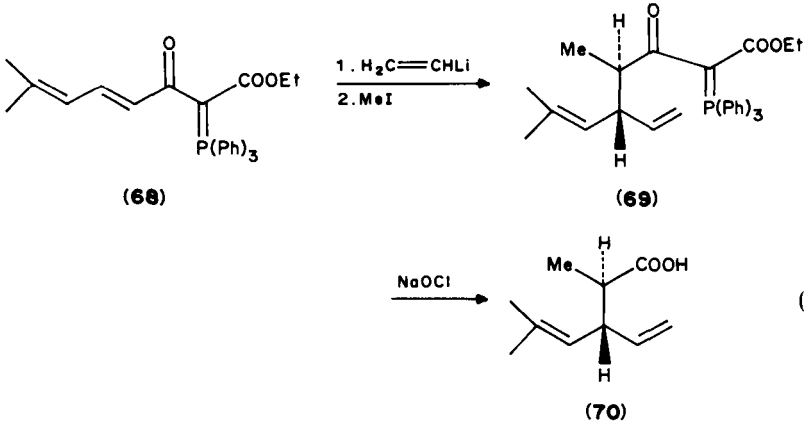
Synthesis of optically active 3-alkylcarboxylic acids via conjugate addition of lithium dialkylcuprates to chiral α-carbonyl α,β-ethylenic sulfoxides is illustrated in equation 738 by the preparation of (*R*)-(+)-3-nonanoic acid (**67**) in 53% chemical yield and 65% optical purity from (*S*)-(+)-(*E*)-1-octenyl sulfoxide (**66**)[1627].



(738)

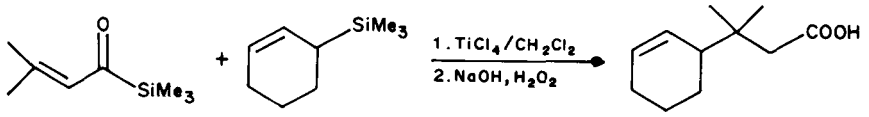
In addition to the Michael acceptors outlined above, chiral α,β-unsaturated oxazolines[1628], aldimines[1629] and oxazepines[1630] have been used in enantioselective syntheses of carboxylic acids and acid derivatives.

Unsaturated acylcarbalkoxytriphenylphosphoranes such as **68** undergo 1,4-addition with organolithium reagents to form intermediate ylide anions, which can be trapped by electrophiles to give 2,3-disubstituted acylphosphoranes **69**. Oxidative cleavage of **69** with sodium hypochlorite affords 2,3-disubstituted carboxylic acids **70** (equation 739)[1631].



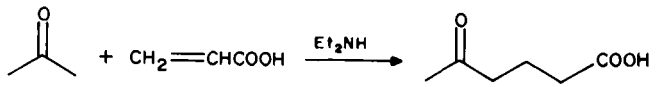
(739)

As an alternative to 1,4-addition of nucleophiles to α,β-unsaturated carbonyl compounds as a route to 3-alkyl carboxylic acids, the titanium chloride-promoted addition of allylsilanes to α,β-unsaturated acylsilanes illustrated in equation 740 can be used[1632]. Similar reactions of allyl- or allenylsilanes with α,β-ethylenic acyl cyanides give rise to δ,ε-ethylenic (or acetylenic) acids respectively[1633].



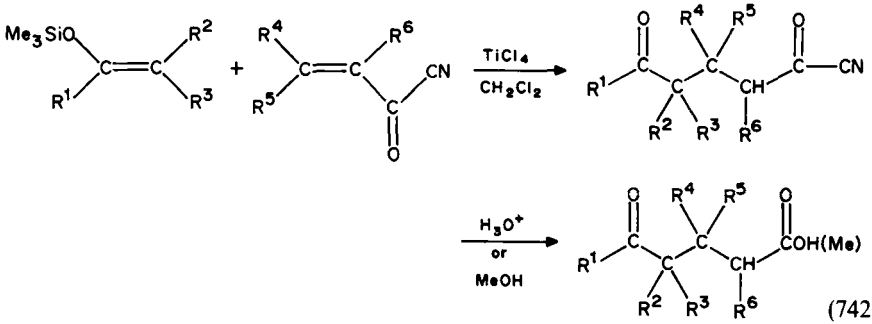
(740)

5-Oxocarboxylic acids and esters are often prepared via conjugate addition of ketone enolates, or their equivalents, to α,β-unsaturated acids or esters. These reactions are frequently carried out by heating a mixture of the ketone, α,β-unsaturated acid and an amine (equation 741)[1634].



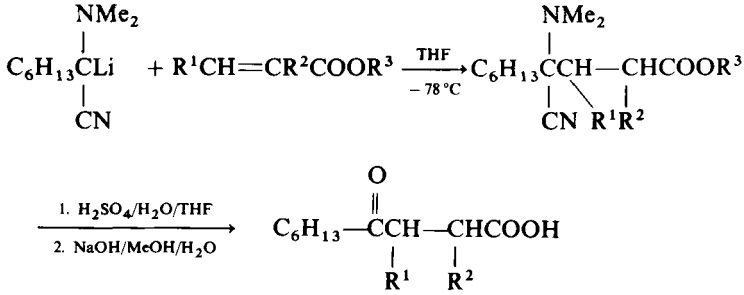
(741)

Conjugate addition of silyl enol ethers to ethylenic acyl cyanides in the presence of titanium tetrachloride leads to 5-oxocarboxylic acids or methyl esters following hydrolysis or methanolysis of the intermediate 5-oxoacyl cyanides (equation 742)[1635].



(742)

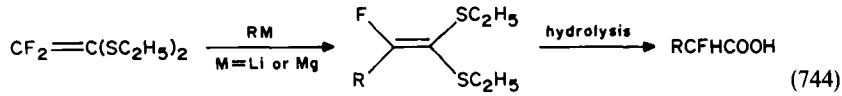
4-Oxocarboxylic acids can be synthesized by conjugate addition of metalated α-aminonitriles to α,β-unsaturated esters followed by acid hydrolysis of the amino and nitrile functions to generate the 4-keto group, and then saponification of the ester (equation 743)[1636].



(743)

R^1 = H, Me, Ph, H
R^2 = H, H, H, Me

α-Monofluroalkanoic acids can be prepared in good yields by reaction of difluroketene thioacetal, prepared from trifluroacetaldehyde thioacetal by means of LDA, with various organometallic reagents (RM), followed by hydrolysis of the resulting monofluroketene thioacetals (equation 744)[1637].

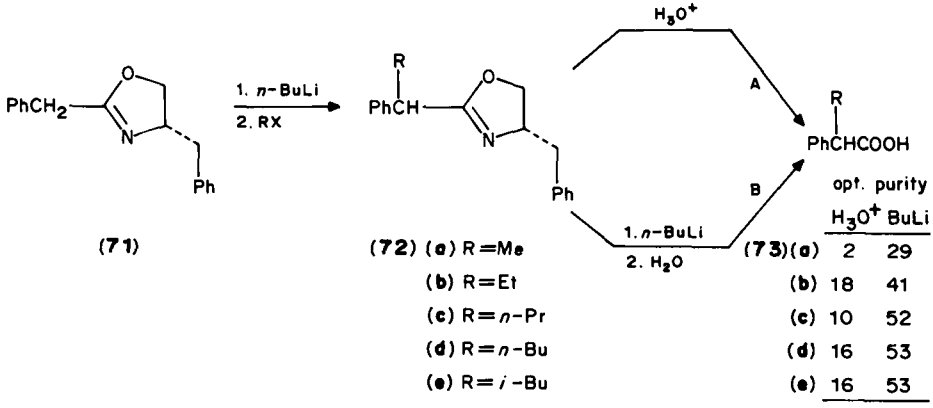


(744)

*11. From oxazolines

Applications of chiral 2-(α,β-unsaturated alkyl) oxazolines in Michael additions leading to chiral acids have been mentioned earlier[1628]. The use of chiral oxazolines in the asymmetric syntheses of dialkylacetic acids, 3,3-dialkylpropionic acids, esters and lactones has been reviewed[1638].

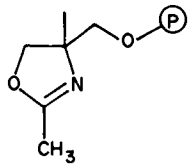
As described in Section II.B.11, the general oxazoline-based approach to chiral dialkylacetic acids consists of lateral deprotonation of a chiral 2-alkyloxazoline, alkylation of the resulting carbanion, and hydrolysis of the oxazoline moiety to give the free acid. When (4*S*)-(−)-2,4-dibenzyl-2-oxazoline (**71**) was subjected to this reaction using methyl, ethyl, *n*-proproyl, *n*-butyl, and isobutyl halides to produce alkylated oxazolines **72a–e**, subsequent hydrolysis of these intermediates gave the respective carboxylic acids **73a–e** in low optical purity (Scheme 9, Pathway A). However, when **72a–e** were



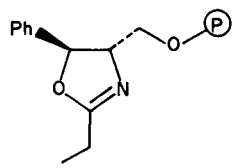
SCHEME 9

deprotonated with *n*-butyllithium, reprotonated with water and then subjected to acidic hydrolysis (Scheme 9, Pathway B), the resulting α-substituted phenylacetic acids showed significantly enhanced optical purity. This process, designated as 'asymmetric transformation', also operates with analogous 2-(α-chloroalkyl)-2-oxazolinones[1639]. A study of the mechanism of such optical enrichment has been published recently[1640].

Carboxylic acids and esters have been synthesized using polymer-bound oxazolines **74** and **75** prepared from 2,4-dimethyl-4-(hydroxymethyl)-2-oxazoline and chloromethylated poly(styrene-*co*-divinylbenzene) and from *trans*-(4*S*,5*S*)-2-ethyl-4-(hydroxymethyl)-2-oxazoline attached to chloromethylated 2% cross-linked polystyrene, respectively[1641]. These polymer-bound reagents were utilized in the same fashion as monomeric oxazolines.



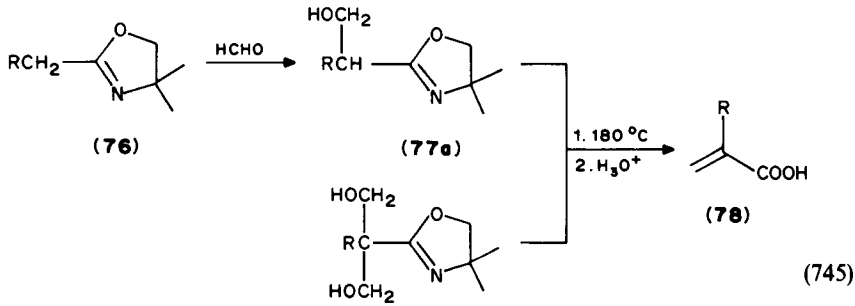
(74)



(75)

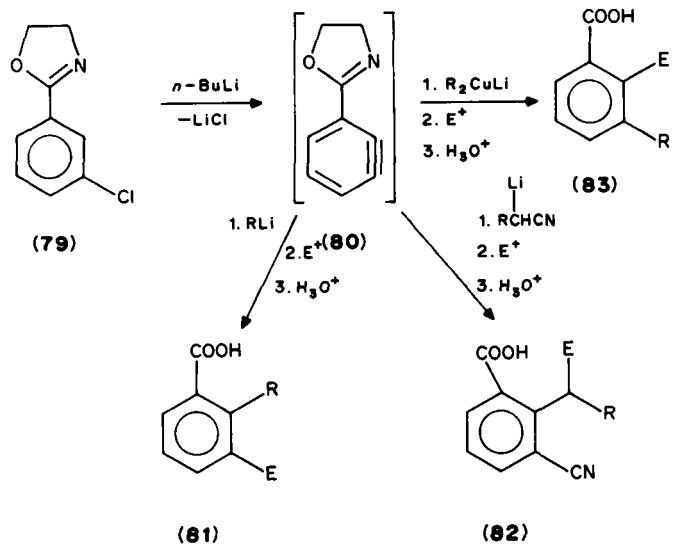
Metalation of the 2-alkyl group was followed by alkylation and hydrolysis or alcoholysis to give the free acid (ester) and the respective polymer-bound amino alcohols, which are then reconverted to **74** and **75** by reaction with the appropriate imino ester. Yields of several achiral acids derived from **74** were satisfactory, but generally lower than those obtained from the monomeric oxazoline. The optical yield (56%) and chemical yield (43–48%) of (*S*)-(+)-ethyl 2-methyl-3-phenylpropanoate resulting from metalation, benzylation and ethanolysis of **75** were each *ca* 10 percent lower than those obtained from comparable solution procedures with the monomeric oxazoline counterpart of **75**. The synthetic potential of **75** is also diminished by sluggish and incomplete hydrolysis of the elaborated oxazoline moiety.

A convenient three-step procedure for the synthesis of α-substituted acrylic acids **78** based on oxazoline chemistry is illustrated in equation 745[1642]. Reaction of a 2-alkyl-2-oxazoline (**76**), possessing an α-methylene group, with paraformaldehyde in the presence of 10% alcoholic potassium hydroxide produces a mixture of mono- and dimethylol derivatives **77a–b**. Heating the mixture of **77a–b** at 180 °C with azeotropic removal of water results in retroaldol condensation and dehydration to give the respective 2-(α-alkylvinyl)-2-oxazolines, which afford α-alkylacrylic acids **78** upon acidic hydrolysis.



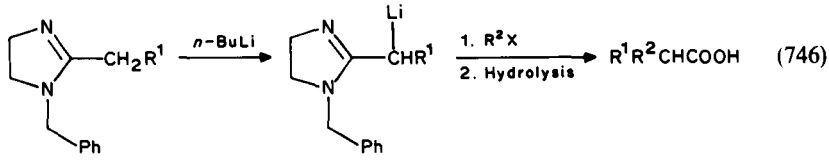
(745)

Initial utilization of 2-aryloxazolines in the synthesis of substituted benzoic acids has led to numerous other applications of these compounds in regiocontrolled aromatic substitution[1643]. A key intermediate in the synthesis of substituted benzoic acids is the benzyne-oxazoline (**80**), which can be generated *in situ* from 2-(*m*-chlorophenyl)-2-oxazoline (**79**). The synthetic versatility of **80** is outlined in Scheme 10. Reaction of **80** with organolithium reagents, followed by addition of electrophiles and hydrolysis of the oxazoline function, produces benzoic acids **81**[1644]. α-Lithio nitriles react with **80** to give, after protonation or electrophilic quenching and hydrolysis, benzoic acids **82**[1645]. Organocuprates add to the *meta*-position of benzyne **80** to ultimately afford benzoic acids **83**[1646].



SCHEME 10

In a procedure similar to the oxazoline protocol for carboxylic acid synthesis, 1-benzyl-2-alkyl-4,5-dihydroimidazoles (**84**) can be converted to the lateral lithio derivatives **85**. Alkylation of **85**, followed by hydrolysis of the elaborated dihydroimidazoles, affords the respective alkanoic acids (equation 746)[1647].



(746)

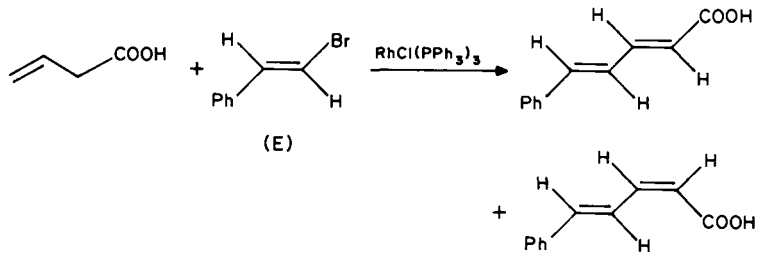
*12. *Coupling reactions*

The coupling reaction of Grignard reagents with ω-bromo acid salts has been adapted to the synthesis of ω-hydroxycarboxylic acids through utilization of Grignard reagents containing an acid-labile hydroxy protecting group, R (equation 747)[1648].

$$Br(CH_2)_nCO_2M + RO(CH_2)_mMgX \longrightarrow \xrightarrow{H_3O^+} HO(CH_2)_{m+n}COOH \qquad (747)$$

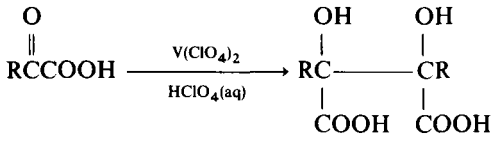
3-Butenoic acid potassium salts react with vinyl halides in the presence of phosphine complexes of rhodium or nickel as catalysts to form conjugated dienoic acids (equation 748)[1649].

Tartaric acids **87a–c** have been prepared in excellent yields by reductive dimerization to form single (undesignated) diastereomers of pyruvic (**86a**), phenylglyoxylic (**86b**) and



(748)

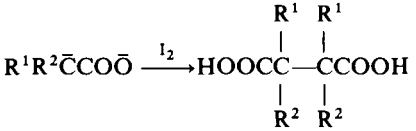
phenylpyruvic acid (**86c**) in the presence of vanadium(II) perchlorate (equation 749)[1650].



(749)

(**86**) (**a**) R = ME (**87a–c**)
(**b**) R = Ph
(**c**) R = $PhCH_2$

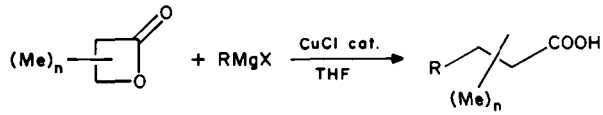
Several recent studies[1651–1653] have dealt with the optimization and mechanism of the iodine promoted dimerization of carboxylic acid dianions to form substituted succinic acids (equation 750).



(750)

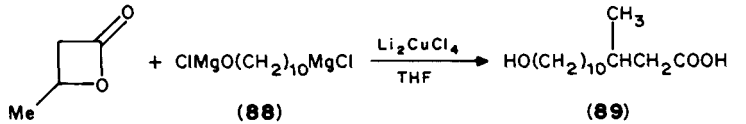
Although reactions of β-propiolactones with organocuprates[1590] were discussed earlier (Section II.A.7) as a method for dealkylative cleavage of esters, copper(I)-catalyzed reactions of Grignard reagents with β-propiolactones, β-vinyl-β-propiolactones and β-ethynyl-β-propiolactones may also be viewed as a versatile type of coupling reaction in which the lactone derivatives serve as the electrophilic reactant.

Grignard reagents, in the presence of copper(I) catalysts, react regiospecifically at the β carbon of propiolactone, α- and β-methylpropiolactone and α,α-dimethylpropiolactone to give β-substituted carboxylic acids in good yields (equation 751)[1654,1655]. Similar ring-opening reactions occur with organolithium reagents[1655]. A convenient one-step



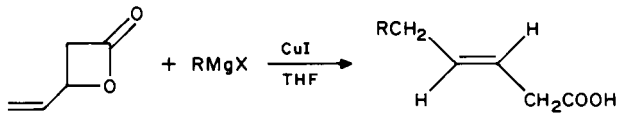
(751)

synthesis of ω-hydroxy carboxylic acids **89** is available through copper(I)-catalyzed reactions of ω-metaloxylated Grignard reagents (**88**) with β-propiolactones (equation 752)[1656].



(752)

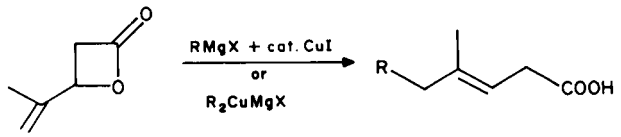
When β-vinyl-β-propiolactone (**90**) is allowed to react with Grignard reagents in the presence of copper(I) catalysts or with diorganocuprates, S_N2' displacement occurs at the terminal carbon of the β-vinyl group to afford (*E*)-3-alkenoic acids in good yields (equation



(753)

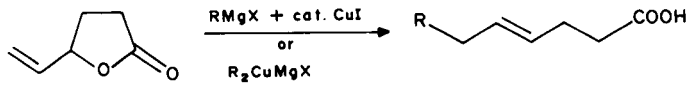
(**90**)

753)[1657]. Similar reactions of β-isopropenyl-β-propiolactone occur through the S_N2' pathway to produce 4-methyl-3-alkenoic acids with a predominance of the (*E*)-isomers (equation 754)[1658]. γ-Vinyl-γ-butyrolactone and δ-vinyl-δ-valerolactone react in similar



(754)

S_N2' fashion with Grignard reagents or with diorganocuprates to afford predominately (*E*)-4-alkenoic acids (equation 755) and (*E*)-5-alkenoic acids (equation 756)[1659].



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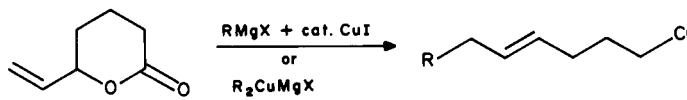
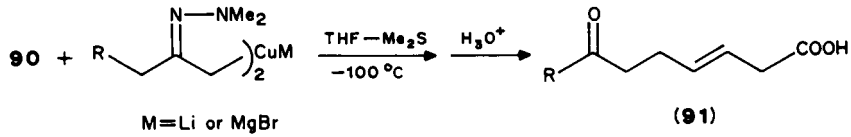
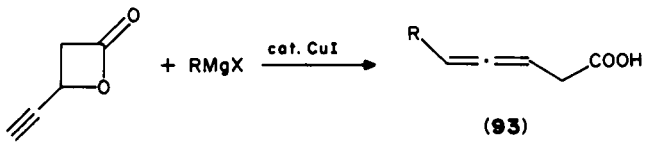


(756)

Reaction of β-vinyl-β-propiolactone (**90**) with cuprate and bromomagnesium derivatives of *N*,*N*-dimethylhydrazones of various aldehydes and ketones results in S_N2' attack of these enolate equivalents at the β-carbon of the exocyclic vinyl group. Hydrolysis with aqueous acid produces 7-oxo-(*E*)-3-alkenoic acids (**91**) as the major products (equation 757)[1660].



β-Ethynyl-β-propiolactone (**92**) undergoes copper(I)-catalyzed S_N2' reactions with Grignard reagents to afford 3,4-alkadienoic acids **93** (equation 758)[1661].

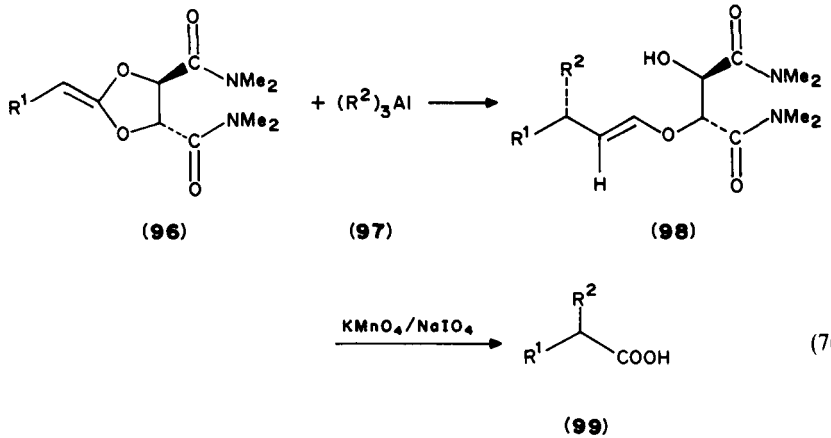


(92) (93) (758)

In contrast to the S_N2' reactions of lactones possessing an exocyclic, unsaturated group, (*Z*)-4-hexenolide **94** reacts with diorganocuprates mainly via the S_N2 mechanism to yield (*Z*)-4-alkenoic acids **95** (equation 759)[1661].

(94) (95) (759)

α,β-Unsaturated acetals **96** derived from (*R,R*)-tartaric acid diamide undergo diastereoselective S_N2' reaction with trialkylaluminum reagents **97** to form enol ethers **98**. Subsequent oxidative cleavage of **98** with potassium permanganate/sodium periodate gives rise to optically active acids **99** (equation 760)[1663].



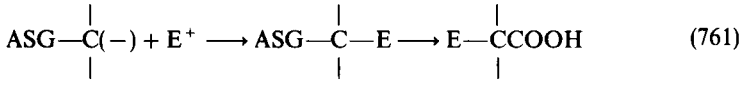
(96) (97) (98) (760)

(99)

*13. *Miscellaneous condensation reactions*

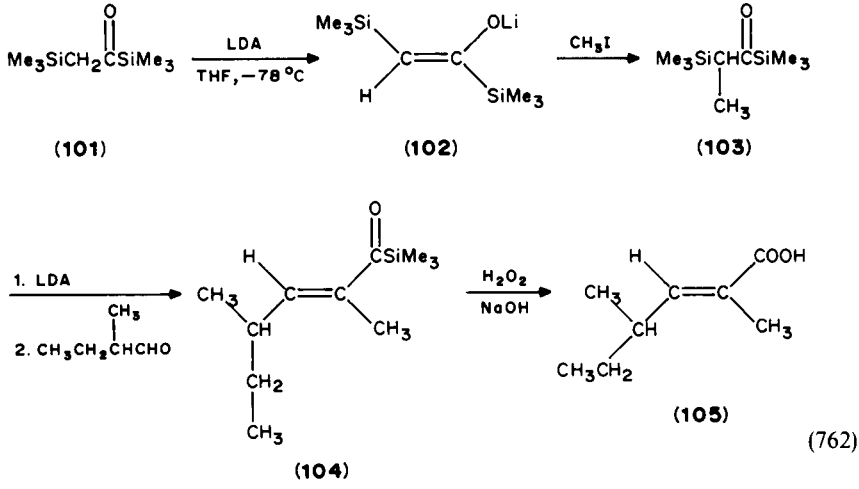
a. *Carbanion reactions.* This section is devoted to a discussion of reactions in which carbanion intermediates derived from active hydrogen substrates other than malonic ester and its derivatives (Section II.B.7), acetoacetic ester (Section II.B.6), carboxylic acids (Section II.B.8) and esters (Section III.B.7) are used in the synthesis of carboxylic acids. This area of research has been an active one during the past decade, especially as applied to the synthesis of chiral carboxylic acids and acid derivatives. The reactions discussed here involve formation of carbanions, generalized by structure **100**, in which the anion-stabilizing group (ASG) is a latent carboxyl function and, in some cases, also a chiral

auxiliary. Reaction of **100** with electrophilic reagents followed by transformation of the ASG into the carboxyl group completes the synthetic sequence (equation 761).



(761)

Deprotonation of [(trimethylsilyl)acetyl]trimethylsilane (**101**) with LDA produces enolate **102**, predominately as the *E* isomer. Alkylation of **102** with methyl and ethyl iodides or allylic and benzylic bromides affords α-substituted [(trimethylsilyl)acetyl]trimethylsilanes **103** as shown in equation 762 using methyl iodide

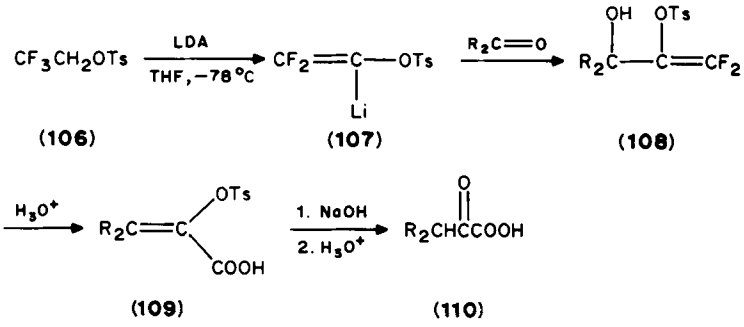


(762)

as the alkylating agent. Deprotonation of **103**, addition of 2-methylbutanal, and spontaneous elimination from the intermediate aldol product leads to the E-disubstituted α,β-unsaturated acylsilane **104**. Cleavage of **104** with alkaline hydrogen peroxide affords (*E*)-2,4-dimethyl-2-hexenoic acid (**105**) in 93% yield[1664]. Treatment of **104** and related α,β-unsaturated acylsilanes with tetrabutyl-ammonium fluoride in the presence of formic acid converts them into α,β-unsaturated aldehydes.

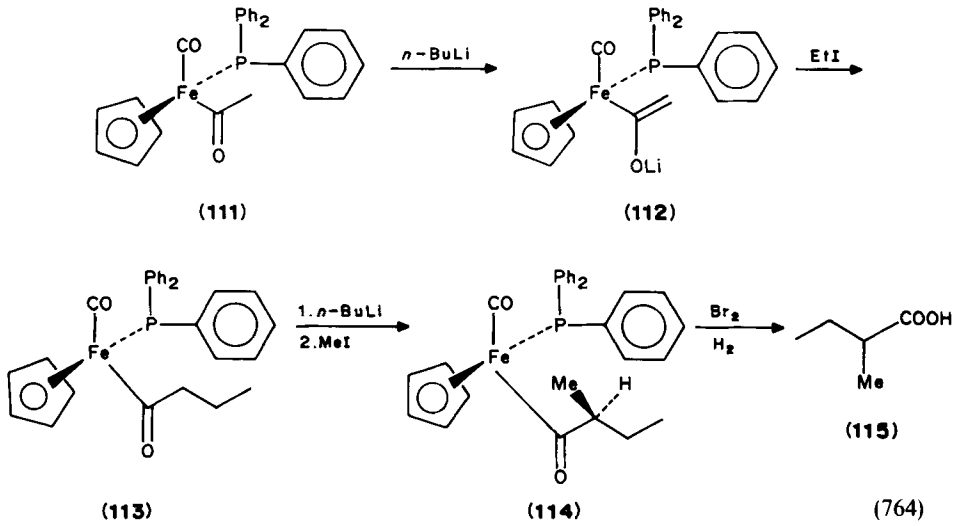
α-Keto acids can be synthesized from 2,2-difluoro-1-tosyllithium (**107**), as illustrated in equation 763[1665]. In this vinyl carbanion-based scheme, **107** is prepared from 2,2,2-trifluoroethyl tosylate (**106**) by means of two equivalents of lithium diisopropylamide. Reaction of **107** with aldehydes or ketones gives carbinols **108**, which are then hydrolyzed with concentrated sulfuric acid to unsaturated tosyloxy acids **109**. Hydrolysis of **109** with aqueous sodium hydroxide followed by acidification affords α-keto acids **110**.

Considerable recent activity has revolved around the use of enolates derived from acyl ligands attached to the chiral auxiliary $[(\eta^5\text{-}C_5H_5)Fe(CO)PPh_3]$. Since numerous synthetic applications of these intermediates have been detailed in a recent review[1666], the following examples are presented as a sample of their utility in carboxylic acid synthesis.



(763)

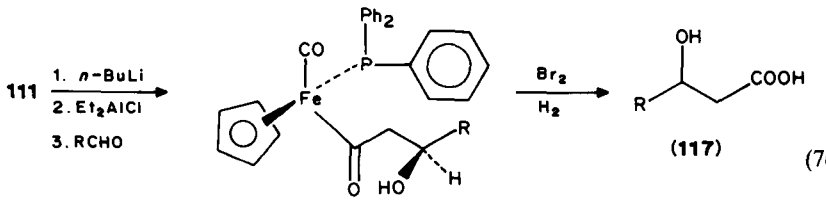
The lithium enolate (**112**), derived from racemic complex **111** (*R* enantiomer shown) by means of *n*-butyllithium, undergoes smooth monoalkylation with various alkyl halides. Thus alkylation of **112** with ethyl iodide gives the propyl acyl complex **113** (equation 764). Subsequent depronation and methylation of **113** affords diastereomer **114** (*R,R* shown) and its enantiomer (*S,S*) with a diastereoselectivity of greater than 200:1 over the accompanying *R,S/S,R* enantiomeric pair. Decomplexation of **114** yields 2-methylbutanoic acid (**115**) in excellent overall yield. It should be noted that acid **115** is racemic, since all intermediates leading to it are racemates.



(764)

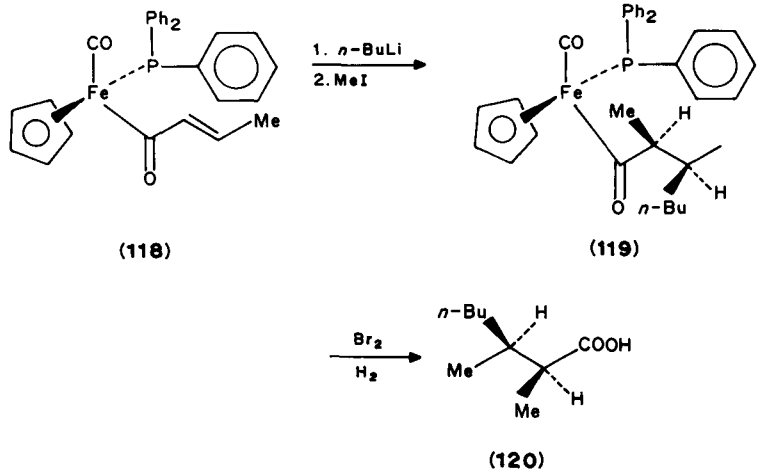
Aldol condensation between the aluminum enolate corresponding to **112** (Li = $AlEt_2$) and aldehydes proceeds with greater than 100:1 diastereoselectivity to give racemic adducts **116** with the stereochemistry shown in equation 765. Decomplexation then gives hydroxy acids. Use of the corresponding tin enolate reverses the diastereoselectivity, while the lithium enolate shows limited diastereoselectivity.

Tandem conjugate addition–alkylation reactions with α,β-unsaturated acyl complexes such as **118**, prepared by Peterson olefination of acetyl complex **111**, produce carboxylic acids with two new stereocenters in high diastereoselective yield. For example, conjugate



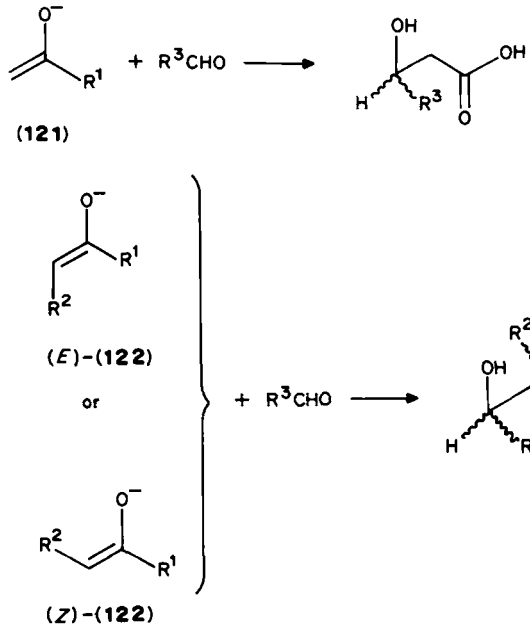
(765)

addition of *n*-butyllithium to **118**, followed by alkylation of the resulting enolate with methyl iodide, affords complex **119** possessing the indicated stereochemistry. Decomplexation of **119** gave *erythro* acid **120** (equation 766). Sequential treatment of (*S*)-**118**, generated *in situ* from optically pure (*S*)-(+)-**111**, with *n*-butyllithium and methyl iodide, followed by oxidative decomplexation with bromine in the presence of benzylamine gave the *N*-benzyl amide of (2*R*),(3*R*)-(−)-**120**, $[\alpha]_D^{24}$ 5.3° (*ca* 1.23, C_6H_6) in 81% yield.



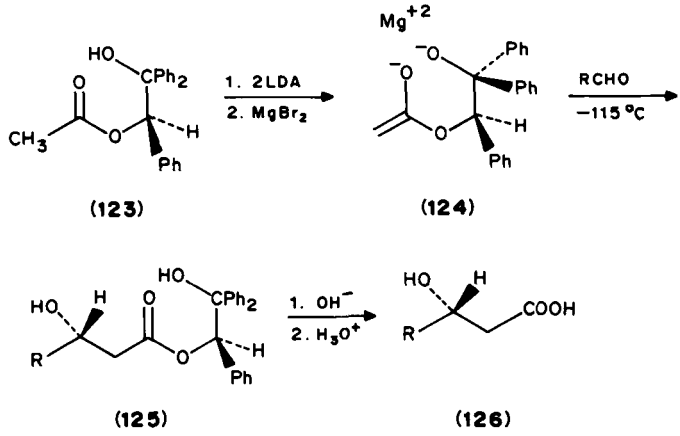
(766)

β-Hydroxy acids and their derivatives can, in principle, be synthesized by aldol condensation of an aldehyde (RCHO) with an appropriate enolate (**121** or **122**) in which R^1 is O^- (acid dianion), OR (ester enolate),—NR_2 (carboxamide enolate) or some other group which can ultimately be transformed into a carboxyl or carboxylate function (equation 767). Such reactions are accompanied by several interesting stereochemical problems. In the case of enolates **121**, which have no α-substituents, a subject of recent interest has been the possibility of establishing enantioselectivity at the new stereocenter. With α-substituted enolates **122**, which can exist in *Z* and/or *E* configurations, the stereochemical consequences of aldol condensations become more complicated because two stereocenters are generated during carbon–carbon bond formation. Several comprehensive reviews dealing with the stereochemistry of aldol condensations have appeared since 1981[1667–1670], and the interested reader is referred to these for detailed discussions. The following examples represent several useful and stereochemically predictable aldol condensations for the synthesis of β-hydroxy acids and β-hydroxy acid derivatives.



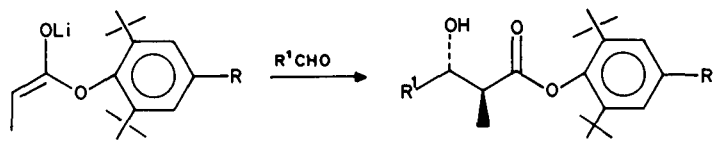
(767)

Synthetic equivalents of the chiral acetate enolate (**121**, R^1 = chiral auxiliary) have generally proven to be less enantioselective in aldol condensations than their α-alkyl counterparts (**122**, R^1 = chiral auxiliary)[1669-1672]. Recently, however, the magnesium dianion (**124**) of (*R*)-2-acetoxy-1,1,2-triphenylethanol (**123**) has been shown to react with aldehydes to form β-hydroxy esters **125** in diastereomeric excesses (de) of 92–97%. Saponification of these mixtures afforded the respective optically active β-hydroxy acids **126** in correspondingly high optical purity (equation 768)[1673].



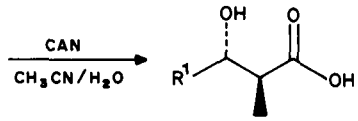
(768)

Condensations of *E*-enolates **127a–b** containing bulky phenoxy groups with aldehydes occur to produce exclusively *threo*, or so-called *anti*[1674], aldol products **128**. Oxidative cleavage of **128** with ceric ammonium nitrite (CAN) affords *anti* β-hydroxy acids **129**



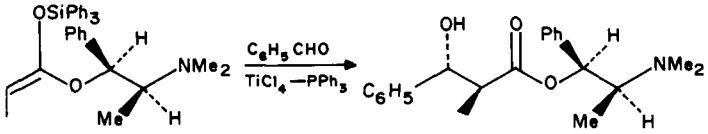
(127) (a) R=Me
(b) R=OMe

(128)



(129) (769)

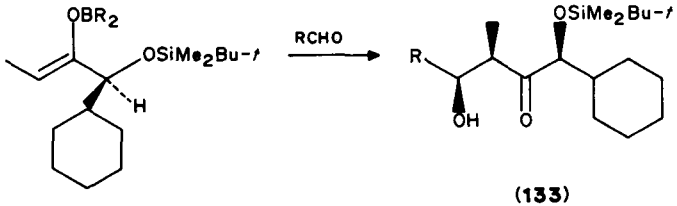
(equation 769)[1675]. In a related aldol procedure, reaction of the *E*-silyl ketene acetal (**130**) derived from 1*R*,2*S*-*N*-methylephedrine propionate with benzaldehyde in the presence of titanium tetrachloride–triphenylphosphine complex gives the *anti* β-hydroxy ester **131** in 90% chemical yield and 94% ee (equation 770)[1676]. At present this procedure is limited to aromatic and conjugated aldehydes; nonconjugated aldehydes react sluggishly or not at all.



(130) (770)

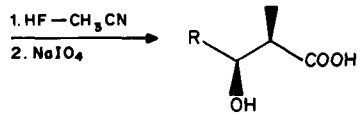
(131)

Chiral boron enolates (**132**) prepared from (*S*)-1-*tert*-butyldimethylsiloxy-1-cyclohexylbutan-2-one react with achiral aldehydes to give almost exclusively the *syn* aldol products **133** (equation 771)[1677]. Subsequent desilylation and sodium metaperiodate oxidation completes the enantioselective synthesis of β-hydroxy acids **134**. The (*R*) analog of **132** leads, by the same sequence of steps, to enantiomers of **134**.



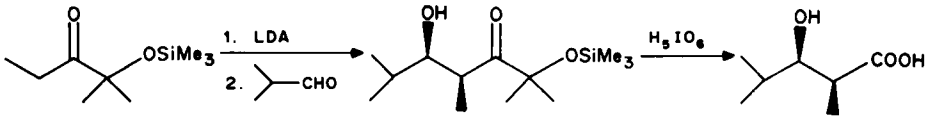
(132)

(133)



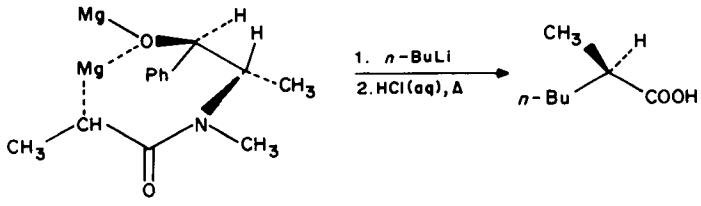
(134) (771)

Achiral lithium enolates related to **132** can be carried through a similar series of reactions to yield racemic β-hydroxy acids of high diastereomeric purity as shown in equation 772 by the synthesis of (2*SR*, 3*RS*)-2,4-dimethyl-3-hydroxypentanoic acid (**136**)[1678].



(**135**) (**136**) (772)

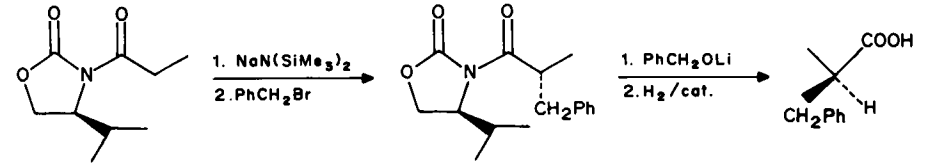
Asymmetric syntheses of α-substituted carboxylic acids can be accomplished by alkylation of enolates derived from chiral *N*,*N*-disubstituted amides. An illustration of this protocol is given in equation 773 by the synthesis of (*S*)-(−)-2-methylhexanoic acid (**138**) in 68% chemical yield and 78% optical yield from the magnesium enolate (**137**) of *N*-acetyl-1-ephedrin[1679].



(773)

(**137**) (**138**)

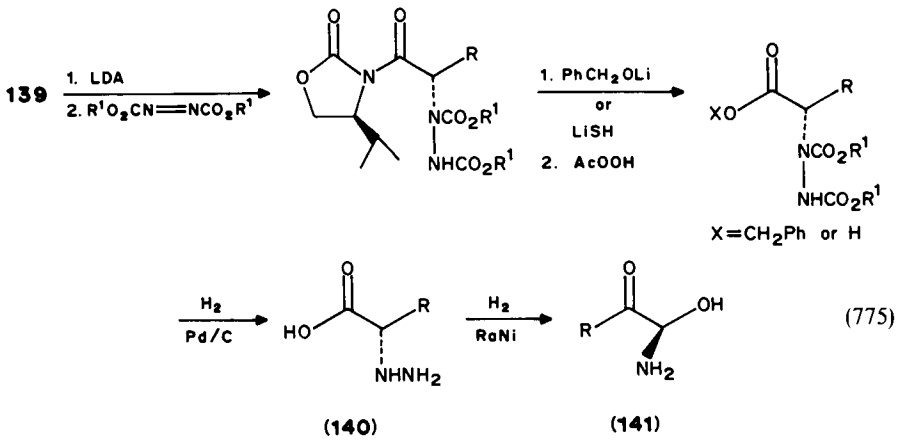
Asymmetric alkylation of chiral imide enolates[1680–1684] furnishes a useful synthetic approach to chiral α-substituted carboxylic acids as shown by the preparation of (*R*)-(−)-2-methyl-3-phenylpropanoic acid from chiral oxazolidone **139** (equation 774)[1681]. Chiral



(**139**) (774)

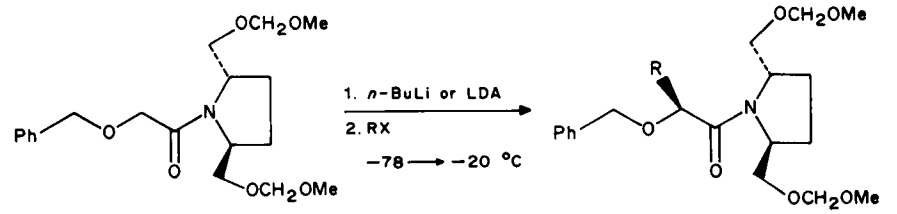
imide **139** and related chiral *N*-acyl oxazolidones can also be employed in the synthesis of optically active α-hydrazino acids (**140**) and α-amino acids (**141**) (equation 775)[1685].

Chiral α-hydroxy acids can be synthesized by lithiation, alkylation and hydrolysis of (2*S*,5*S*)-*N*-(benzyloxyacetyl)-*trans*-2,5-bis(methoxymethoxymethyl)pyrrolidine (**142**) (equation 776)[1686]. An alternative carbanion route to chiral α-hydroxy acids involves generation and alkylation of α-anions derived from 2-substituted 1,3-dioxolane-4-ones prepared from chiral mandelic acids[1687]. Thus, lithiation of **143** followed by alkylation with methyl iodide and hydrolysis gave (*S*)-(+)-atrolactic acid (**144**) with ee of 85% (equation 777). Analogous 1,3-dioxolane-4-ones (**143**, Ph = Me) derived from chiral lactic acid behave similarly, but with lower chemical and optical yields[1687,1688].



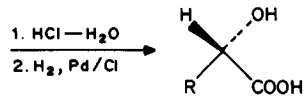
(775)

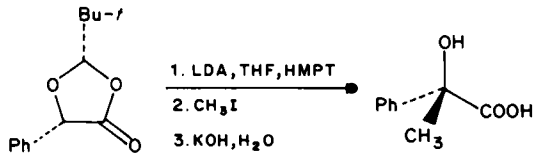
(140) (141)



(142)

(776)



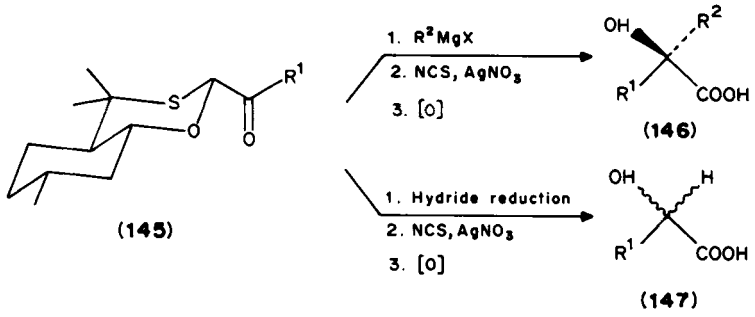


(777)

(143) (144)

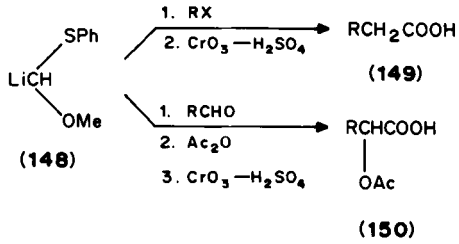
Chiral 2-acyl-1,3-oxathianes (**145**) can serve as precursors to chiral tertiary (**146**)[1689] and secondary (**147**)[1690] α-hydroxy acids as shown in equation 778.

Sulfur-stabilized carbanions continue to play an important role in various synthetic manipulations[1691,1692] including several recent approaches to the preparation of carboxylic acids and their derivatives. For example, treatment of the lithio carbanion **148**, derived from methoxy(phenylthio)methane, with alkyl halides followed by direct oxidation of the elaborated phenylthio derivative with Jones reagent leads to alkylated acetic



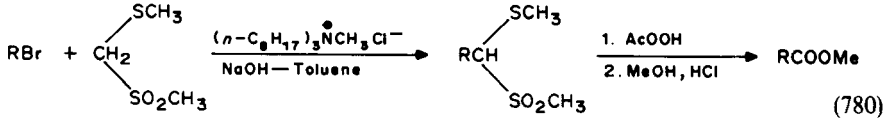
(778)

acids **149**. Reaction of **148** with aldehydes or ketones, acetylation of the intermediate aldol product, and similar oxidation affords α-acetoxy acids **150** (equation 779)[1693]. Carboxylic



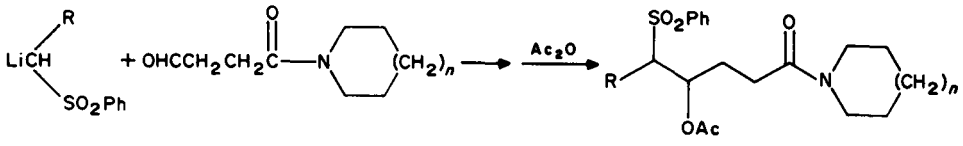
(779)

esters with one more carbon, rather than the two additional carbons that usually accompany carbanion preparations, can be synthesized by alkylation of the carbanion of formaldehyde dimethyl dithioacetal *S,S*-dioxide (**151**) under phase-transfer conditions to give *C*-alkyl derivatives **152**. Treatment of **152** with peracetic acid followed by hydrogen chloride in refluxing methanol leads to a Pummerer-type rearrangement and methanolysis to afford esters **153** (equation 780)[1694].



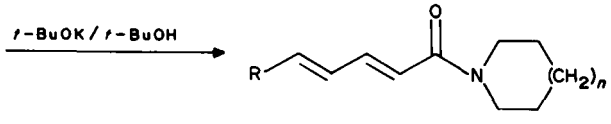
(780)

α-Lithio derivatives of simple alkyl phenyl sulfones can be employed in the stereoselective synthesis of (2*E*,4*E*)-dienamides **156** and (2*E*,4*E*)-dienoates (**159**). The former products are prepared by initial reaction of aldehyde carboxamides **154a–b** with such carbanions, followed by *in situ* acetylation of the resulting adducts to give 4-acetoxy-5-phenylsulfonyl amides **155a–b**. Double elimination reaction of **155a–b** employing potassium *tert*-butoxide as a base proceeds in a stereoselective manner to give dienamides **156a–b** (equation 781)[1695]. Reaction of α-lithio sulfones with aldehyde ester **157**, conversion of the resulting aldol product to lactone **158**, double elimination of **158** and esterification yields dienoates **159** (equation 782)[1695].



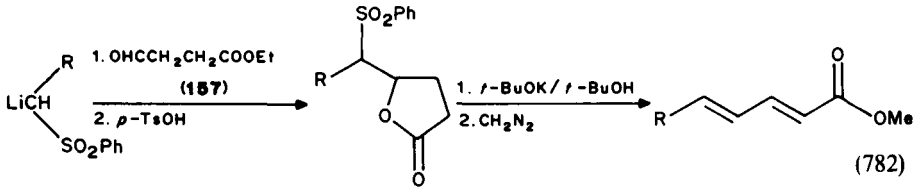
(154) (a) $n=1$
(b) $n=0$

(155) (a) $n=1$
(b) $n=0$



(781)

(156) (a) $n=1$
(b) $n=0$

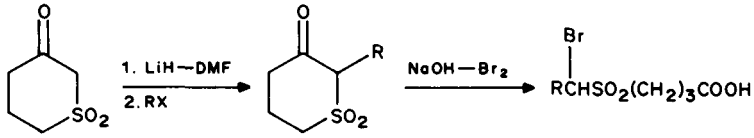


(782)

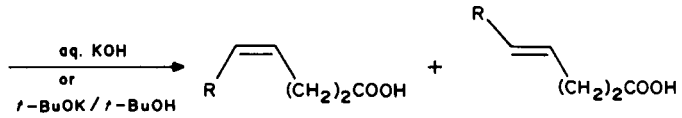
(158) (159)

Reactions of analogous sulfonyl-stabilized carbanions with succinic anhydride afford 4-oxo-5-phenylsulfonyl acids[1696].

The carbanion derived from tetrahydrothiopyran-3-one 1,1-dioxide (**160**) functions as a four-carbon synthon in the preparation of (*Z*)- or (*E*)-α,β-unsaturated acids **163** and **164**, respectively[1697]. Thus, deprotonation of **160** by means of lithium hydride, followed by alkylation, affords *C*-alkylated keto sulfones **161** accompanied by *ca* 25 percent of the *O*-



(160) (161) (162)

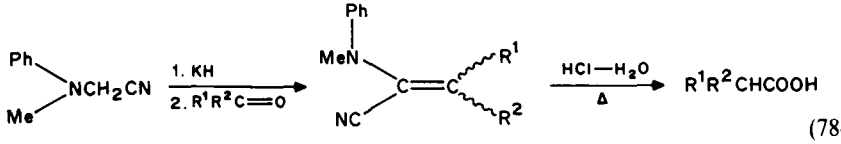


(783)

(163) (164)

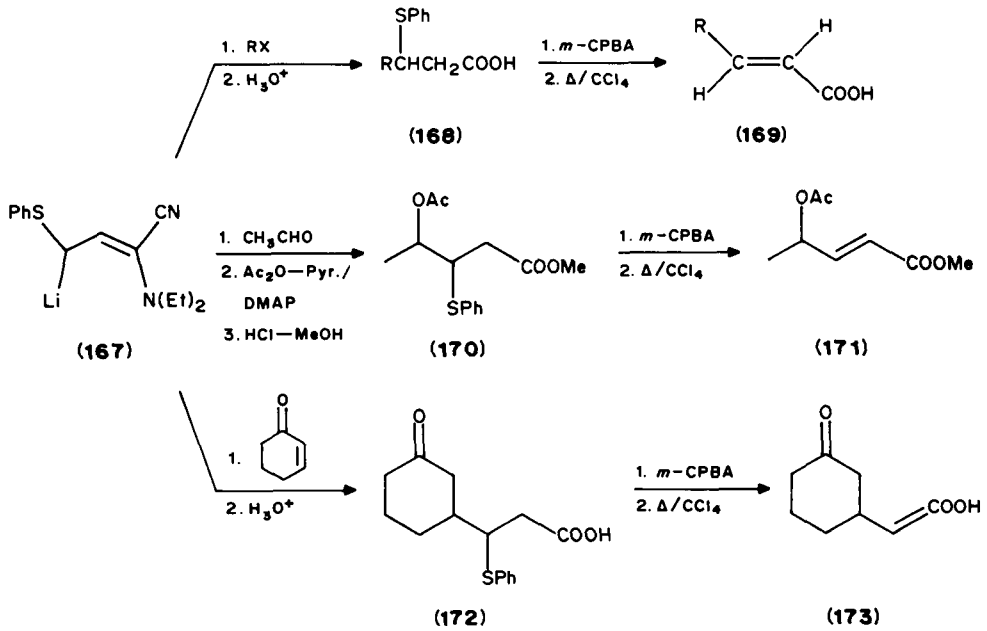
alkylated products. Ring-opening bromination of **161** provides α-bromosulfone acids **162**, which can be converted stereoselectively to **163** and **164** by Ramberg–Backlund rearrangement (equation 783)[1697]. Rearrangement of **162** using aqueous potassium hydroxide favors formation of (*Z*)-acids **163**, while potassium *tert*-butoxide in refluxing *tert*-butyl alcohol gives predominately (*E*)-acids **164**.

An efficient sequence for one-carbon homologation of aldehydes and benzophenone to carboxylic acids involves deprotonation of α-(*N*-methylanilino)acetonitrile (**165**), reaction of the derived anion with the appropriate carbonyl compound to form α-cyanoenamines **166**, and acid hydrolysis of **166** to form the respective carboxylic acids (equation 784)[1698]. Alternatively, the carbanion of **165** can be reacted with trimethylsilyl chloride to form the α-trimethylsilyl derivative, which can then be subjected to olefination and hydrolysis.



(165) (166) (784)

γ-Lithio α-cyanoenamine **167** can act as the equivalent of a β-carboxy vinyl anion via the series of reactions shown in Scheme 11[1699]. Alkylation of **167**, followed by acidic hydrolysis of the cyanoenamine function, produces β-phenylthio acids **168**, which can then be converted to (*E*)-α,β-unsaturated acids **169** by oxidative elimination. Reaction of **167** with acetaldehyde, followed by acylation in the presence of 4-dimethylaminopyridine,

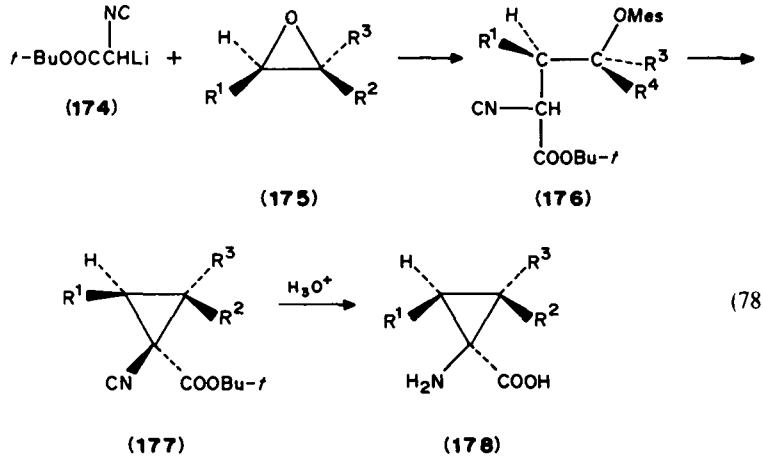


(167) (168) (169) (170) (171) (172) (173)

SCHEME 11

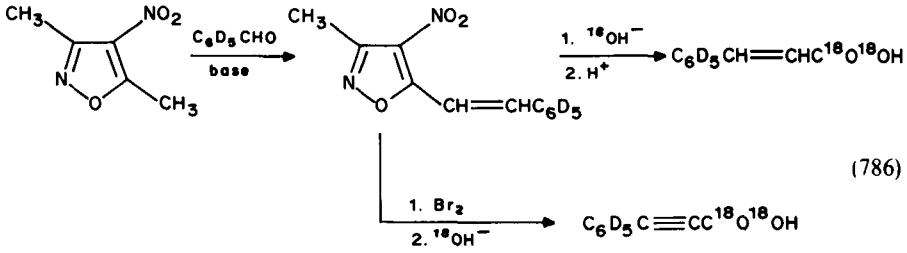
DMAP, and esterification of the resulting product, affords β-phenylthio-γ-acetoxy ester **170**, which undergoes oxidative desulfurization to yield α,β-unsaturated ester **171**. Reaction of **167** with cyclohexenone produces the 1,4-product **172**, which can then be converted to unsaturated acid **173**.

A recent application of metalated isonitriles to the synthesis of biologically active 1-amino-1-cyclopropanecarboxylic acids (**178**) involves reaction of α-lithio *tert*-butyl isocyanoacetate (**174**) with epoxides **175** to produce, after mesylate formation, intermediates **176**. Ring closure of **176** proceeds in diasteroselective fashion to give *tert*-butyl 1-isocyano-1-cyclopropanecarboxylates **177**, which are hydrolyzed to **178** (equation 785)[1700].



(785)

A recent example of the utility of carbanions derived from alkyl isoxazoles in carboxylic acid synthesis[1701,1702] is illustrated by the synthesis of ^{18}O-bilabelled cinnamic acid and 3-phenyl-2-propenoic acid (equation 786)[1703].



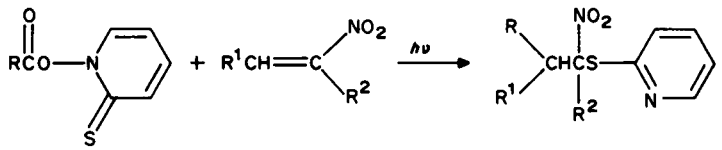
(786)

*C. Acids by Free-radical Processes

*1. Radical additions to unsaturated systems

Several recent reviews have addressed the use of radical additions to unsaturated systems for the synthesis of nonpolymeric organic compounds including carboxylic acids and their derivatives[1704,1705]. An interesting method, not mentioned in these reviews,

involves addition of radicals derived from thiohydroxamic esters **179** to nitroolefins **180** to give α-nitrosulfides **181**. Oxidation of certain of these adducts ($R^2 = H$) with alkaline hydrogen peroxide affords α,α-disubstituted acids **182** (equation 787)[1706].



(179) **(180)** **(181)**

$$\xrightarrow[K_2CO_3]{H_2O_2} RR^1CHCOOH \qquad (787)$$

(182)

*D. Acids by Hydrocarboxylation Reactions

Reactions which introduce the —COOH group into organic molecules by reaction with carbon monoxide are classified as hydrocarboxylations, and are usually accomplished by the use of a metal catalyst. Several metal catalysts dominate this field of carboxylic acid synthesis and for that reason the information presented will be categorized essentially alphabetically by the metal catalyst used.

Cobalt compounds such as cobalt acetate and cobalt carbonyl have been reported in the recent literature to catalyze the addition of carbon monoxide to alcohols, alkyl, aryl and vinyl halides, and heteroaromatic halides, to produce the corresponding carboxylic acids. A general reaction sequence which can be used to illustrate these reactions is illustrated in equation 788, and involves the reaction of a substrate with gaseous carbon monoxide at pressures ranging from 1 to 136 atmospheres (14.7 to 2,000 psi), in the presence of a cobalt catalyst under other appropriate reaction conditions.

$$\text{substrate} + CO\ (\text{atm}) + \text{Co catalyst} \xrightarrow[\text{conditions}]{\text{other}} \text{carboxylic acid products(s)} \qquad (788)$$

Table 60 lists the current literature information dealing with cobalt-catalyzed carbon monoxide additions which produce carboxylic acids.

Carbonylcopper(I) and carbonylsilver(I) ions, which are formed by reaction of copper(I) oxide or silver monoxide with carbon monoxide in strong acid media (equation 789), have been used to hydrocarboxylate olefins, dienes, alcohols and saturated hydrocarbons to produce the corresponding carboxylic acids. Since these reactions are performed in strong acid solutions, and since the substrates used are easily protonated, they usually proceed via initial carbocation formation followed by carbon monoxide addition to produce the carboxylic acid (equation 790).

$$M_2O + \text{strong acid} + CO \rightarrow M(I)(CO)_n \qquad (789)$$
$$M = Cu, n = 3 \text{ or } 4$$
$$M = Ag, n = 2$$

$$\text{substrate} + \text{acid} + M(CO)_n \xrightarrow[\text{conditions}]{\text{other}} \text{carboxylic acid product(s)} \qquad (790)$$

Table 61 lists the current literature information dealing with copper- and silver-catalyzed hydrocarboxylation reactions which produce carboxylic acids.

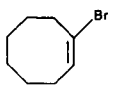
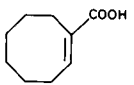
TABLE 60. Cobalt-catalyzed hydrocarboxylation reactions

Substrate	Cobalt catalyst	CO pressure (units)	Reaction time (h)	Reaction temp. (°C)	Other conditions	Products (ratio)	Yield (%)	Reference
n-BuBr	$Co_2(CO)_8$	800 psi	—	96	aq. Me_3COH, NaOH, LiI, bis (1,2-diphenylphosphino) ethane	*n*-C_4H_9COOH + *n*-$C_4H_9COCOOH$	50 20	1707
PhCl	$CoCRACO^{a,b}$	1 atm	52	63	1) THF 2) H_3O +	$PhCOOCH_2CMe_3$ + PhCOOH (20/80)	35–40	1708
PhCl	$Co_2(CO)_8$	1 atm	13	65	aq. NaOH, benzene, $Bu_4N^+Br^-$, *hν*(350 nm)	None	0	1709
PhBr	$CoCRACO^{a,c}$	1 atm	20	63	1) THF 2) H_3O +	None	0	1708
PhBr	$CoCRACO^{a,d}$	1 atm	3	63	1) THF 2) H_3O +	PhCOOEt + PhCOOH (55/45)	20–25	1708
PhBr	$CoCRACO^{a,d}$	1 atm	40	40	1) THF 2) H_3O +	PhCOOEt + PhCOOH (65/35)	50–55	1708
PhBr	$CoCRACO^{a,b}$	1 atm	20	63	1) THF 2) H_3O +	$PhCOOCH_2CMe_3$ + PhCOOH (85/15)	80–85	1708
PhBr	$CoCRACO^{a,e}$	1 atm	40	63	1) THF 2) H_3O +	$PhCOOC_8H_{17}$ + PhCOOH (25/75)	30–35	1708
PhBr	$CoCRACO^{a,f}$	1 atm	42	63	1) THF 2) H_3O +	$PhCOOC_6H_{11}$-*c* + PhCOOH (45/55)	65–70	1708
PhBr	$CoCRACO^{a,g}$	1 atm	40	63	1) THF 2) H_3O +	$PhCOOCHMeC_6H_{13}$ + PhCOOH (85/15)	80–55	1708
PhBr	$CoCRACO^{a,h}$	1 atm	24	63	1) THF 2) H_3O +	$PhCOOC_5H_{11}$-*t* + PhCOOH (75/25)		1708
PhBr	$CoCRACO^{a,i}$	1 atm	42	63	1) THF 2) H_3O +	$PhCOOC_4H_9$-*t* + PhCOOH (80/20)	70–75	1708
PhBr	$CoCRACO^{a,j}$	1 atm	95	63	1) THF 2) H_3O +	$PhCOOCH_2CH{=}CH_2$ + PhCOOH (0/100)	55–60	1708
PhBr	$CoCRACO^{a,b}$	1 atm	10	63	1) THF 2) H_3O +	$PhCOOCH_2CMe_3$ + PhCOOH (45/55)	80–85	1708
PhBr	$CoCRACO^{a,b}$	1 atm	45	63	1) THF 2) H_2O +	$PhCOOCH_2CMe_3$ + PhCOOH (70/30)	80–85	1708
PhBr	$Co_2(CO)_8$	1 atm	1.5	65	aq. NaOH, benzene, $Bu_4N^+Br^-$, *hν*(350 nm)	PhCOOH	95	1709
PhBr	$Co_2(CO)_8$	1 atm	12	32	aq. NaOH, benzene, $Bu_4N^+Br^-$, *hν*(350 nm)	PhCOOH	97	1709
PhBr	$EtO_2CCH_2Co(CO)_4$	1 atm	1–2	25	NaOH, MeOH	PhCOOH	45	1710
PhBr	$Co_2(CO)_8$	1 atm	—	15–20	Ca(OH), EtOH, Me_2SO_4	PhCOCOOH + PhCOOH (61/10)	70	1714

(*continued*)

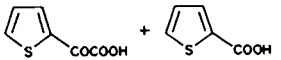
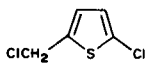
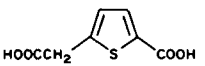
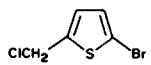
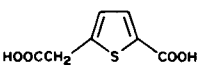
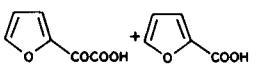
TABLE 60. (*continued*)

Substrate	Cobalt catalyst	CO pressure (units)	Reaction time (h)	Reaction temp. (°C)	Other conditions	Products (ratio)	Yield (%)	Reference
PhBr	$Co_2(CO)_8$	1 atm	—	40	Ca(OH), EtOH, Me_2SO_4	PhCOCOOH + PhCOOH (1/10)	98.3	1714
PhBr	$Co_2(CO)_8$	1 atm	—	55	$Ca(OH)_2$, EtOH, Me_2SO_4	PhCOCOOH + PhCOOH (0/100)	—	1714
PhBr	$Co_2(CO)_8$	1 atm	—	15–20	$Ca(OH)_2$, MeOH, Me_2SO_4	PhCOCOOH + PhCOOH (1/5)	78.2	1714
PhBr	$Co_2(CO)_8$	1 atm	—	15–20	$Ca(OH)_2$, *n*-PrOH, Me_2SO_4	PhCOCOOH + PhCOOH (90/1)	29	1714
PhBr	$Co_2(CO)_8$	1 atm	—	15–20	$Ca(OH)_2$, *t*-BuOH, Me_2SO_4	PhCOCOOH + PhCOOH	Trace	1714
PhBr	$Co_2(CO)_8$	1 atm	—	15–20	$Ca(OH)_2$, EtOH, MeI	PhCOCOOH + PhCOOH (82/10)	70.4	1714
PhI	CoCRACO[a,b]	1 atm	1	63	1) THF 2) H_3O +	$PhCOOCH_2CMe_3$ + PhCOOH (10/90)	70–75	1708
p-TolBr	CoCRACO[a,b]	1 atm	20	63	1) THF 2) H_3O +	*p*-$TolCOOCH_2CMe_3$ + *p*-TolCOOH (60/40)	90–95	1708
p-TolBr	$Co_2(CO)_8$	1 atm	1.5	65	aq. NaOH, benzene, $Bu_4N^+Br^-$, *hv*(350 nm)	*p*-TolCOOH	97	1709
p-TolBr	CoCRACO[a,b]	1 atm	45	63	1) THF 2) H_3O +	*p*-$TolCOOCH_2CMe_2$ + *p*-TolCOOH (55/45)	70–75	1708
o-TolBr	CoCRACO[a,b]	1 atm	25	63	1) THF 2) H_3O +	*o*-$TolCOOCH_2CMe_3$ + *o*-TolCOOH (45/55)	80–85	1708
o-TolBr	$Co_2(CO)_8$	1 atm	2.25	65	aq. NaOH, benzene, $Bu_4N^+Br^-$, *hv*(350 nm)	*o*-TolCOOH	96	1709
m-TolBr	CoCRACO[a,b]	1 atm	20	63	1) THF 2) H_3O +	*m*-$TolCOOCH_2CMe_3$ + *m*-TolCOOH (45/55)	85–90	1708
m-TolBr	$Co_2(CO)_8$	1 atm	—	15–20	$Ca(OH)_2$, EtOH, Me_2SO_4	*m*-TolCOCOOH + *m*-TolCOOH (52/10)	62.6	1714
p-AnBr	CoCRACO[a,b]	1 atm	15	63	1) THF 2) H_3O +	*p*-$AnCOOCH_2CMe_3$ + *p*-AnCOOH (55/45)	95–100	1708
p-AnBr	CoCRACO[a,b]	1 atm	45	63	1) THF 2) H_3O +	*p*-$AnCOOCH_2CMe_3$ + *p*-AnCOOH (45/55)	55–60	1708
p-AnBr	$Co_2(CO)_8$	1 atm	2	65	aq. NaOH, benzene, $Bu_4N^+Br^-$, *hv*(350 nm)	*p*-AnCOOH	94	1709
p-AnBr	$Co_2(CO)_8$	1 atm	—	15–20	$Ca(OH)_2$, EtOH, Me_2SO_4	*p*-AnCOCOOH + *p*-AnCOOH (16/10)	43.2	1714

p-AnBr	$Co_2(CO)_8$	1 atm		10	$Ca(OH)_2$, EtOH, Me_2SO_4	*p*-AnCOCOOH + *p*-AnCOOH (55/10)	21.9	1714
o-AnBr	CoCRACO[a,b]	1 atm	15	63	1) THF 2) H_3O^+	*o*-$AnCOOCH_2CMe_3$ + *o*-AnCOOH (60/40)	95–100	1708
o-AnBr	$Co_2(CO)_8$	1 atm	2	65	aq. NaOH, benzene, $Bu_4N^+Br^-$, *hv* (350 nm)	*o*-AnCOOH	47	1709
m-AnBr	CoCRACO[a,b]	1 atm	15	63	1) THF 2) H_3O^+	*m*-$AnCOOCH_2CMe_3$ + *m*-AnCOOH (55/45)	90–95	1708
p-FC_6H_4Br	CoCRACO[a,b]	1 atm	20	63	1) THF 2) H_3O^+	*p*-$FC_6H_4COOCH_2CMe_3$ + *p*-FC_6H_4COOH (55/45)	85–90	1708
p-FC_6H_4Br	CoCRACO[a,b]	1 atm	50	63	1) THF 2) H_3O^+	*p*-$FC_6H_4COOCH_2CMe_3$ + *p*-FC_6H_4COOH (55/45)	65–70	1708
p-FC_6H_4Br	$Co_2(CO)_8$	1 atm	—	15–20	$Ca(OH)_2$, EtOH, Me_2SO_4	*p*-$FC_6H_4COCOOH$ + *p*-FC_6H_4COOH (19/10)	82.5	1714
p-ClC_6H_4Br	$Co_2(CO)_8$	1 atm	1	65	aq. NaOH, benzene, $Bu_4N^+Br^-$, *hv* (350 nm)	*p*-ClC_6H_4COOH	98	1709
p-$MeCOC_6H_4Br$	CoCRACO[a,b]	1 atm	25	63	1) THF 2) H_3O^+	*p*-$MeCOC_6H_4COOCH_2CMe_3$ + *p*-$MeCOC_6H_4COOH$ (55/45)	80–85	1708
p-$MeCOC_6H_4Br$	CoCRACO[a,b]	1 atm	60	63	1) THF 2) H_3O^+	*p*-$MeCOC_6H_4COOCH_2CMe_3$ + *p*-$MeCOC_6H_4COOH$ (55/45)	65–70	1708
p-$Me_2NC_6H_4Br$	CoCRACO[a,b]	1 atm	15	63	1) THF 2) H_3O^+	*p*-$Me_2NC_6H_4COOCH_2CMe_3$ + *p*-$Me_2NC_6H_4COOH$ (10/90)	35–40	1708
	$Co_2(CO)_8$	1 atm	5	65	aq. NaOH, benzene, $Bu_4N^+Br^-$, *hv* (350 nm)		98	1709
$C_6H_5CH{=}CHBr$	$Co_2(CO)_8$	1 atm	8	65	aq. NaOH, benzene, $Bu_4N^+Br^-$, *hv* (350 nm)	$C_6H_5CH{=}CHCOOH$	62	1709
1,3,5-trichlorobenzene	$Co_2(CO)_8$	1 atm	20	65	NaOH, H_2O, EtOH, *hv*	Benzene-1,3,5-tricarboxylic acid + Benzene-1,2-dicarboxylic acid	85.5 11.9	1712
1-Naphthyl bromide	$Co_2(CO)_8$	1 atm	5	65	aq. NaOH, benzene, $Bu_4N^+Br^-$, *hv* (350 nm)	1-Naphthanoic acid	96	1709
1-Naphthyl chloride	$Co_2(CO)_8$	1 atm	—	15	$Ca(OH)_2$, EtOH, Me_2SO_4	1-Naph COCOOH + 1-NaphCOOH (28/10)	76.4	1714
2-Bromo-6-hydroxy-naphthalene	$EtO_2CCH_2Co(CO)_4$	1 atm	1–2	25	NaOH, MeOH	6-Hydroxynaphthalene-2-carboxylic acid	48	1710
3-Bromopyridine	$PhCH_2Co(CO)_4$[k]	1 atm	1–2	35	NaOH, MeOH	Pyridine-3-carboxylic acid	55	1710

(*continued*)

TABLE 60. (*continued*)

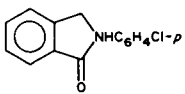
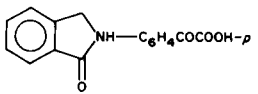
Substrate	Cobalt catalyst	CO pressure (units)	Reaction time (h)	Reaction temp. (°C)	Other conditions	Products (ratio)	Yield (%)	Reference
	$Co_2(CO)_8$	1 atm	—	15–20	$Ca(OH)_2$, EtOH, Me_2SO_4	 (13/10)	96	1714
	*l*	—	—	20–30	$Ca(OH)_2$, $MeOH/H_2O$		33	1710
	*l*	—	—	20–30	$Ca(OH)_2$, $MeOH/H_2O$		50	1710
	$Co_2(CO)_8$	1 atm	—	10	$Ca(OH)_2$, $EtOH/H_2O$, Me_2SO_4	 (12/10)	74.5	1714
$PhCH_2Cl$	$NaCo(CO)_4$	—	—	—	—	$PhCH_2COOH$	87.1	1713
$PhCH_2Cl$	$Co_2(CO)_8$	1 atm	—	60	Benzyl ether, aq. NaOH, $PhCH_2\overset{+}{N}Et_3Cl^-$	$PhCH_2COOH$	60	1715
$PhCH_2Cl$	$Co_2(CO)_8$	1 atm	6.5	65	aq. NaOH, benzene, Et_3N, $h\nu$(350 nm)	$PhCH_2COOH$	85	1717
$PhCH_2Br$	$Co_2(CO)_8$	1 atm	10–12	25	NaOH, benzyl ether, benzene, $PhCH_2\overset{+}{N}Et_3Cl^-$	$PhCH_2COOH$	85	1716
$PhCH_2Br$	$Co_2(CO)_8$	1 atm	2	65	aq. NaOH, benzene, Et_3N, $h\nu$(350 nm)	$PhCH_2COOH$	85	1717
p-$TolCH_2Cl$	$Co_2(Co)_8$	1 atm	—	60	Benzyl ether, aq. NaOH, $PhCH_2\overset{+}{N}Et_3Cl^-$	*p*-$TolCH_2COOH$ + *p*-TolCHCOCOOH | *p*-$TolCH_2$ (70/30)	75	1717
p-$TolCH_2Br$	$Co_2(CO)_8$	1 atm	2	65	aq. NaOH, Benzene, Et_3N, $h\nu$(350 nm)	*p*-$TolCH_2COOH$	80	1717
o-$TolCH_2Cl$	$Co_2(CO)_8$	1 atm	—	60	Benzyl ether, aq. NaOH, $PhCH_2\overset{+}{N}Et_3Cl^-$	*o*-$TolCH_2COOH$ + *o*-TolCH-COCOOH | *o*-$TolCH_2$ (60/40)	78	1715

o-TolCH$_2$Br	$Co_2(CO)_8$	1 atm	10–12	25	NaOH, benzyl ether, benzene, $PhCH_2\overset{+}{N}Et_3Cl^-$	*o*-TolCHCOCOOH | *o*-TolCH$_2$	30	1716
o-TolCH$_2$Br	$Co_2(CO)_8$	1 atm	5	65	aq. NaOH, benzene, Et_3N, *hν* (350 nm)	*o*-TolCH$_2$COOH	25	1717
m-TolCH$_2$Cl	$Co_2(CO)_8$	1 atm	—	60	benzyl ether, aq. NaOH, $PhCH_2\overset{+}{N}Et_3Cl^-$	*m*-TolCH$_2$COOH + *m*-TolCHCOCOOH | *m*-TolCH$_2$ (82/18)	58	1715
p-NCC$_6$H$_4$CH$_2$Br	$Co_2(CO)_8$	1 atm	10–12	25	NaOH, benzyl ether, benzene/ $PhCH_2\overset{+}{N}Et_3Cl^-$	*p*-HOOCC$_6$H$_4$CH$_2$COOH	50	1716
m-CF$_3$C$_6$H$_4$CH$_2$Cl	$Co_2(CO)_8$	1 atm	—	60	Benzyl ether, aq. NaOH, $PhCH_2\overset{+}{N}Et_3Cl^-$	*m*-CF$_3$C$_6$H$_4$CH$_2$COOH	34	1715
2,4,6-Me$_3$C$_6$H$_2$CH$_2$Cl	$Co_2(CO)_8$	1 atm	—	60	Benzyl ether, aq. NaOH, $PhCH_2\overset{+}{N}Et_3Cl^-$	2,4,6-Me$_3$C$_6$H$_2$CH$_2$COOH + 2,4,6-Me$_3$C$_6$H$_2$CH$_2$COCOOH (50/50)	21	1715
2-NaphCH$_2$Br	$Co_2(CO)_8$	1 atm	10–12	25	NaOH, benzyl ether, benzene, $PhCH_2\overset{+}{N}Et_3Cl^-$	2-NaphCH$_2$COOH	64	1716
$PhCH_2\overset{+}{N}Et_3Br^-$	$Co_2(CO)_8$	1 atm	Overnight	65	aq. NaOH, benzene, $Bu_4\overset{+}{N}Br^-$, *hν* (350 nm)	PhCH$_2$COOH	80	1717
$PhCH_2\overset{+}{N}Et_3Br^-$	$Co_2(CO)_8$	1 atm	Overnight	65	aq. NaOH, Bu_4NBr^-, *hν* (350 nm)	PhCH$_2$COOH	85	1717
$PhCH_2\overset{+}{N}Et_3Cl^-$	$Co_2(CO)_8$	1 atm	Overnight	65	aq. NaOH, benzene, $Bu_4\overset{+}{N}Br^-$, *hν* (350 nm)	PhCH$_2$COOH	85	1717
$PhCH_2\overset{+}{N}Et_3Cl^-$	$Co_2(CO)_8$	1 atm	Overnight	65	aq. NaOH, $Bu_4\overset{+}{N}Br^-$, *hν* (350 nm)	PhCH$_2$COOH	85	1717
p-TolCH$_2\overset{+}{N}Et_3$Br	$Co_2(CO)_8$	1 atm	Overnight	65	aq. NaOH, benzene, $Bu_4\overset{+}{N}Br^-$, *hν* (350 nm)	*p*-TolCH$_2$COOH	85	1717
p-TolCH$_2\overset{+}{N}Et_3Cl^-$	$Co_2(CO)_8$	1 atm	Overnight	65	aq. NaOH, $Bu_4\overset{+}{N}Br^-$, *hν* (350 nm)	*p*-TolCH$_2$COOH	85	1717
o-TolCH$_2\overset{+}{N}Et_3Br^-$	$Co_2(CO)_8$	1 atm	Overnight	65	aq. NaOH, benzene, $Bu_4\overset{+}{N}Br^-$, *hν* (350 nm)	*o*-TolCH$_2$COOH	85	1717
o-TolCH$_2\overset{+}{N}Et_3Br^-$	$Co_2(CO)_8$	1 atm	Overnight	65	aq. NaOH, $Bu_4\overset{+}{N}Br^-$, *hν* (350 nm)	*o*-TolCH$_2$COOH	85	1717
o-TolCH$_2\overset{+}{N}Et_3Cl^-$	$Co_2(CO)_8$	1 atm	Overnight	65	aq. NaOH, benzene, $Bu_4\overset{+}{N}Br^-$, *hν* (350 nm)	*o*-TolCH$_2$COOH	85	1717

(*continued*)

TABLE 60. (*continued*)

Substrate	Cobalt catalyst	CO pressure (units)	Reaction time (h)	Reaction temp. (°C)	Other conditions	Products (ratio)	Yield (%)	Reference
o-TolCH$_2\overset{+}{N}$Et$_3$Cl$^-$	$Co_2(CO)_8$	1 atm	Overnight	65	aq. NaOH, Bu$_4\overset{+}{N}$Br$^-$, *hν*(350 nm)	*o*-TolCH$_2$COOH	85	1717
m-TolCH$_2\overset{+}{N}$Et$_3$Cl$^-$	$Co_2(CO)_8$	1 atm	Overnight	65	aq. NaOH, Bu$_4\overset{+}{N}$Br$^-$, *hν*(350 nm)	*m*-TolCH$_2$COOH	83	1717
p-ClC$_6$H$_4$CH$_2\overset{+}{N}$Et$_3$Cl$^-$	$Co_2(CO)_8$	1 atm	Overnight	65	aq. NaOH, benzene, Bu$_4\overset{+}{N}$Br$^-$, *hν*(350 nm)	*p*-HOOCC$_6$H$_4$CH$_2$COOH	70	1717
p-ClC$_6$H$_4$CH$_2\overset{+}{N}$Et$_3$Cl$^-$	$Co_2(CO)_8$	1 atm	Overnight	65	aq. NaOH, Bu$_4\overset{+}{N}$Br$^-$, *hν*(350 nm)	*p*-HOOCC$_6$H$_4$CH$_2$COOH	75	1717
p-BrC$_6$H$_4$CH$_2\overset{+}{N}$Et$_3$Br$^-$	$Co_2(CO)_8$	1 atm	Overnight	65	aq. NaOH, benzene, Bu$_4\overset{+}{N}$Br$^-$, *hν*(350 nm)	*p*-HOOCC$_6$H$_4$CH$_2$COOH	75	1717
p-BrC$_6$H$_4$CH$_2\overset{+}{N}$Et$_3$Br$^-$	$Co_2(CO)_8$	1 atm	Overnight	65	aq. NaOH, Bu$_4\overset{+}{N}$Br$^-$, *hν*(350 nm)	*p*-HOOCC$_6$H$_4$CH$_2$COOH	80	1717
o-BrC$_6$H$_4$CH$_2\overset{+}{N}$Et$_3$Br$^-$	$Co_2(CO)_8$	1 atm	Overnight	65	aq. NaOH, Bu$_4\overset{+}{N}$Br$^-$, *hν* (350 nm)	*o*-HOOCC$_6$H$_4$CH$_2$COOH	78	1717
p-NCC$_6$H$_4$CH$_2\overset{+}{N}$Et$_3$Br$^-$	$Co_2(CO)_8$	1 atm	Overnight	65	aq. NaOH, Bu$_4\overset{+}{N}$Br$^-$, *hν*(350 nm)	*p*-HOOCC$_6$H$_4$CH$_2$COOH	85	1717
CH$_2$=CHCH$_2\overset{+}{N}$Et$_3$Br$^-$	$Co_2(CO)_8$	1 atm	Overnight	65	aq. NaOH, Bu$_4\overset{+}{N}$Br$^-$, *hν*(350 nm)	MeCH=CHCOOH (*trans*)	80	1717
PhCH=CHCH$_2\overset{+}{N}$Et$_3$Cl$^-$ (*trans*)	$Co_2(CO)_8$	1 atm	Overnight	65	aq. NaOH, benzene, Bu$_4\overset{+}{N}$Br$^-$, *hν*(350 nm)	PhCH=CHCH$_2$COOH (*trans*)	70	1717
PhCHMeBr	$Co_2(CO)_8$	1 atm	—	25	$CaCO_3$, *t*-BuOH, H_2O	PhCHMeCOCOOH	71.6	1714
PhCHMeBr	$Co_2(CO)_8$	1.8 atm	—	25	$CaCO_3$, *t*-BuOH, H_2O	PhCHMeCOCOOH	72.2	1714
PhCHMeBr	$Co_2(CO)_8$	1 atm	–	55	$CaCO_3$, *t*-BuOH, H_2O	PhCHMeCOCOOH	40	1714
PhCHMeBr	$Co_2(CO)_8$	1 atm	–	55	$CaCO_3$, EtOH, H_2O	PhCHMeCOOH + Ph(CH$_2$)$_2$COOH	70	1714

PhCHMeBr	$Co_2(CO)_8$	1.8 atm	–	25	$CaCO_3$, t-$C_5H_{11}OH$, H_2O	PhCHMeCOCOOH	84	1714
PhCHMeCl	$Co_2(CO)_8$	1.8 atm	–	40	$CaCO_3$, t-$C_5H_{11}OH$, H_2O	PhCHMeCOCOOH	38.5	1714
p-(i-Bu)C_6H_4CHMeBr	$Co_2(CO)_8$	1.8 atm	—	10	$CaCO_3$, t-BuOH, H_2O	p-(i-Bu)C_6H_4CHMeCOCOOH	64.6	1714
p-(i-Bu)C_6H_4CHMeCl	$Co_2(CO)_8$	1.8 atm		16	$CaCO_3$, t-BuOH, H_2O	p-(i-Bu)C_6H_4CHMeCOCOOH	61.9	1714
p-(i-Bu)C_6H_4CHMeCl	$Co_2(CO)_8$	1 atm		16	$CaCO_3$, i-PrOH, H_2O	p-(i-Bu)C_6H_4CHMeCOCOOH	46.6	1714
p-(i-Bu)C_6H_4CHMeCl	$Co_2(CO)_8$	1 atm		16	NaOH, t-BuOH, H_2O	p-(i-Bu)C_6H_4CHMeCOCOOH	49.7	1714
p-(i-Bu)C_6H_4CHMeCl	$Co_2(CO)_8$	1 atm		16	LiOH, t-BuOH, H_2O	p-(i-Bu)C_6H_4CHMeCOCOOH	42	1714
	$Co_2(CO)_8$	1 atm		25	$CaCO_3$, t-BuOH, H_2O		40.9	1714

[a] CoCRACO = mixture of NaH, RONa, $Co(OAc)_2$, CO.
[b] RONa = sodium neopentyloxide.
[c] RONa = sodium methoxide.
[d] RONa = sodium ethoxide.
[e] RONa = sodium 1-actyloxide.
[f] RONa = sodium cyclohexyloxide.
[g] RONa = sodium 2-octyloxide.
[h] RONa = sodium t-amyloxide.
[i] RONa = sodium t-butoxide.
[j] RONa = sodium allyloxide.
[k] Catalyst generated 'in situ' by reaction of $Co(CO)_4^-$ with $PhCH_2Cl$.
[l] See Reference 1711.

TABLE 61. Copper- and silver-catalyzed hydrocarboxylation reactions

Substrate	Active metal catalyst	Acid system	Reaction time (h)	Reaction temp. (°C)	Other conditions	Products (ratio)[a]	Yield (%)	Reference
$Me_3CCH{=}CH_2$	$Cu(CO)_4^+$	95% H_2SO_4	—	0	—	Me_2CHCMe_2COOH	89	1718
n-$C_3H_7CMe{=}CH_2$	$Cu(CO)_4^+$	95% H_2SO_4	—	0	—	n-$C_3H_7CMe_2COOH$ + $Et_2CMeCOOH$ + $EtMe_2COOH$	61.1 17.7 10.1	1718
$EtCH{=}CMe_2$	$Cu(CO)_4^+$	95% H_2SO_4	—	0	—	n-$C_3H_7CMe_2COOH$ + $Et_2CMeCOOH$ + $EtCMe_2COOH$	46.3 19.2 15.8	1718
i-$PrCH{=}CHMe$ (*trans*)	$Cu(CO)_4^+$	95% H_2SO_4	—	0	—	n-$C_3H_7CMe_2COOH$ + $Et_2CMeCOOH$ + $EtCMe_2COOH$	58.4 27.5 7	1718
n-$C_3H_7CH{=}CH_2$	$Ag(CO)_2^+$	95% H_2SO_4	2–4	30	—	$EtCMe_2COOH$	74	1719
$Me_3CCH_2CMe{=}CH_2$	$Cu(CO)_3^+$	BF_3–H_2O[b]	—	30	Cyclohexane	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	96	1720
$Me_3CCH_2CMe{=}CH_2$	$Cu(CO)_3^+$	BF_3–H_2O[b]	—	30	Chlorobenzene	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	93	1720
$Me_3CCH_2CMe{=}CH_2$	$Cu(CO)_3^+$	BF_3–H_2O[c]	—	30	Cyclohexane	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	55	1720
$Me_3CCH_2CMe{=}CH_2$	$Cu(CO)_3^+$	BF_3–85% H_3PO_4	—	20	Cyclohexane	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	77	1720
$Me_3CCH_2CMe{=}CH_2$	$Cu(CO)_3^+$	BF_3–85% H_3PO_4	—	20	Chlorobenzene	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	80	1720
$Me_3CCH_2CMe{=}CH_2$	$Cu(CO)_3^+$	BF_3–50% H_3PO_4	—	30	Cyclohexane	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	81	1720
$Me_3CCH_2CMe{=}CH_2$	$Cu(CO)_3^+$	BF_3–50% H_3PO_4	—	30	Cyclohexane	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	83	1720
$Me_3CCH_2CMe{=}CH_2$	$Cu(CO)_3^+$	HF–H_2O[d]	—	18	Cyclohexane	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	98	1720

$Me_3CCH_2CMe{=}CH_2$	$Cu(CO)_3^+$	$HF–H_2O–BF_3$[d]	—	18	Cyclohexane	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	99	1720
$Me_3CCH_2CMe{=}CH_2$	$Cu(CO)_3^+$	$HF–H_2O–BF_3$[d]	—	18	Chlorobenzene	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	95	1720
$Me_3CCH_2CMe{=}CH_2$	$Ag(CO)_2^+$	$BF_3–H_2O$[b]	—	20	Chlorobenzene	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	78	1720
$Me_3CCH_2CMe{=}CH_2$	$Ag(CO)_2^+$	$BF_3–H_2O$[b]	—	20	Cyclohexane	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	80	1720
$Me_3CCH_2CMe{=}CH_2$	$Cu(CO)_3^+$	96% H_2SO_4	—	20	Cyclohexane	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	40	1720
$Me_3CCH_2CMe{=}CH_2$	$Cu(CO)_3^+$	96% H_2SO_4	—	20	Chlorobenzene	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	40	1720
$Me_3CCH_2CMe{=}CH_2$	$Cu(CO)_3^+$	$BF_3–H_2O$[b]	—	20	Cyclohexane + 1-octene	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	73	1720
$Me_3CCH_2CMe{=}CH_2$	$Cu(CO)_3^+$	$BF_3–H_2O$[b]	—	30	—	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	76.9	1720
$Me_3CCH_2CMe{=}CH_2$	$Cu(CO)_3^+$	$BF_3–H_2O$[b]	—	30	Mesitylene	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	84.6	1720
$Me_3CCH_2CMe{=}CH_2$	$Cu(CO)_3^+$	$BF_3–H_2O$[b]	—	30	Chlorocyclohexane	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	49.8	1720
$Me_3CCH_2CMe{=}CH_2$	$Cu(CO)_3^+$	$BF_3–H_2O$[b]	—	30	Fluorobenzene	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	80.4	1720
$Me_3CCH_2CMe{=}CH_2$	$Cu(CO)_3^+$	$BF_3–H_2O$[b]	—	30	Bromobenzene	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	71.2	1720
$Me_3CCH_2CMe{=}CH_2$	$Cu(CO)_3^+$	$BF_3–H_2O$[b]	—	30	CCl_4	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	72.9	1720
$Me_3CCH_2CMe{=}CH_2$	$Cu(CO)_3^+$	$BF_3–H_2O$[b]	—	30	$CHCl_3$	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	66.7	1720

(*continued*)

TABLE 61. (*continued*)

Substrate	Active metal catalyst	Acid system	Reaction time (h)	Reaction temp. (°C)	Other conditions	Products (ratio)[a]	Yield (%)	Reference
$Me_3CCH_2CMe{=}CH_2$	$Cu(CO)_3^+$	BF_3–H_2O[b]	—	30	CH_2Cl_2	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	46.4	1720
$Me_3CCH_2CMe{=}CH_2$	$Cu(CO)_3^+$	BF_3–H_2O[b]	—	30	CH_2ClCH_2Cl	$Me_3CCH_2CMe_2COOH$ + Me_3CCOOH + other acids	54.1	1720
n-$C_4H_9CH{=}CH_2$	$Cu(CO)_4^+$	95% H_2SO_4	—	0	—	$Et_2CMeCOOH$ + n-$C_3H_7CMe_2COOH$	49.8 48.9	1718
n-$C_4H_9CH{=}CH_2$	$Ag(CO)_2^+$	95% H_2SO_4	2–4	30	—	n-$C_3H_7CMe_2COOH$(44) + $Et_2CMeCOOH$(23) + $EtCMe_2COOH$(21)	45	1719
n-$C_4H_9CH{=}CH_2$	$Cu(CO)_3^+$	BF_3–H_2O + BF_3–H_3PO_4	2–4	30	—	n-$C_3H_7CMe_2COOH$(55) + $Et_2CMeCOOH$(45)	83	1719
n-$C_4H_9CH{=}CH_2$	$Cu(CO)_4^+$	BF_3–H_2O	1	25	—	n-$C_3H_7CMe_2COOH$(60) + $Et_2CMeCOOH$(20)	80	1721, 1722
n-$C_3H_7CH{=}CHMe$	$Cu(CO)_4^+$	95% H_2SO_4	—	0	—	n-$C_3H_7CMe_2COOH$ + $Et_2CMeCOOH$	50.8 48.4	1718
n-$C_5H_{11}CH{=}CH_2$	$Ag(CO)_2^+$	95% H_2SO_4	2–4	30	—	n-$C_4H_9CMe_2COOH$(66) + n-$C_3H_7CMeEtCOOH$(25)	62	1719
n-$C_5H_{11}CH{=}CH_2$	$Cu(CO)_3^+$	BF_3–H_2O + BF_3–H_3PO_4	2–4	30	—	n-$C_4H_9CMe_2COOH$(53) + n-$C_3H_7CEtMeCOOH$(47)	87	1719
n-$C_6H_{13}CH{=}CH_2$	$Ag(CO)_2^+$	95% H_2SO_4	2–4	30	—	n-$C_4H_9CMeEtCOOH$(65) + n-$C_5H_{11}CMe_2COOH$(35)	76	1719
n-$C_6H_{13}CH{=}CH_2$	$Ag(CO)_2^+$	BF_3–H_2O + BF_3–H_3PO_4	2–4	30	—	n-$C_4H_9CMeEtCOOH$(68) + n-$C_5H_{11}CMe_2COOH$(32)	83	1719
n-$C_6H_{13}CH{=}CH_2$	$Cu(CO)_3^+$	BF_3–H_2O + BF_3–H_3PO_4	2–4	30	—	n-$C_4H_9CEtMeCOOH$(67) + n-$C_5H_{11}CMe_2COOH$(33)	81	1719
n-$C_6H_{13}CH{=}CH_2$	$Cu(CO)_3^+$	BF_3–H_2O[b]	—	30	Cyclohexane	Mixture of C_9 acids (97) + Mixture of C_5 acids (3)	70	1720
n-$C_6H_{13}CH{=}CH_2$	$Ag(CO)_2^+$	BF_3–H_2O	1	25	—	n-$C_5H_{11}CMe_2COOH$(55) + n-$C_4H_9CEtMeCOOH$(26) + $(n$-$C_3H_7)_2CMeCOOH$(13)	92	1721, 1722
n-$C_7H_{15}CH{=}CH_2$	$Ag(CO)_2^+$	95% H_2SO_4	2–4	30	—	Mixture of C_{10} acids	84	1719
n-$C_7H_{15}CH{=}CH_2$	$Cu(CO)_3^+$	BF_3–H_2O + BF_3–H_3PO_4	2–4	30	—	n-$C_5H_{11}CEtMeCOOH$(50) + n-$C_6H_{13}CMe_2COOH$(26) + n-$C_6H_{13}CHMeCOOH$(15)	55	1719

n-$C_8H_{17}CH{=}CH_2$	$Ag(CO)_2^+$	95% H_2SH_4	2–4	30	—	Mixture of C_{11} acids	86	1719
n-$C_8H_{17}CH{=}CH_2$	$Cu(CO)_3^+$	BF_3–H_2O + BF_3–H_3PO_4	2–4	30	—	n-$C_6H_{13}CEtMeCOOH$(48) + n-$C_7H_{15}CMe_2COOH$(41)	42	1719
n-$C_8H_{17}CH{=}CH_2$	$Ag(CO)_2^+$	BF_3–H_2O	1	25	—	n-$C_7H_{15}CMe_2COOH$(47) + n-$C_6H_{13}CEtMeCOOH$(23) + n-$C_5H_{11}C$(n-Pr)MeCOOH(11)	86	1721, 1722
n-$C_{10}H_{21}CH{=}CH_2$	$Ag(CO)_2^+$	95% H_2SO_4	2–4	30		Mixture of C_{13} acids	84	1719
cyclohexene	$Cu(CO)_4^+$	BF_3–H_2O	1	25	—	1-Methylcyclopentane-carboxylic acid	75	1721, 1722
$Me_3CCH_2CMe{=}CH_2$ + $Me_3CCH{=}CMe_2$	$Cu(CO)_3^+$	$BF_3{\cdot}2ClCH_2COOH$[f] + $BF_3{\cdot}2CH_3COOH$	2–4	30	—	Me_3CCOOH(33) + Mixture of C_9 acids (36) + Mixture of C_{13} acids (11)	47	1719
Methylcyclohexane + n-$C_6H_{13}CH{=}CH_2$	$Cu(CO)_4^+$	BF_3–H_2O	2	25	—	1-Methylcyclohexane-carboxylic acid + C_9 t-carboxylic acid	30 60	1721, 1722
Methylcyclopentane + n-$C_4H_9CHMeOH$	$Ag(CO)_2^+$	BF_3–H_2O	2	25	—	1-Methylcyclopentane-carboxylic acid + C_7 t-carboxylic acid	30 50	1721, 1722
Me_2CHOH	$Cu(CO)_4^+$	BF_3–H_2O	72	25	—	$Me_2CHCOOH$	15	1721, 1722
Me_3COH	$Ag(CO)_2^+$	95% H_2SO_4	2–4	30	—	Me_3CCOOH(65) + C_9 acids (32)	30	1719
Me_3COH	$Ag(CO)_2^+$	$BF_3{\cdot}2ClCH_2COOH$[f] + $BF_3{\cdot}2CH_3COOH$	2–4	30	—	C_9 acids (50) + C_{13} acids (14)	26	1719
Me_3COH	$Cu(CO)_3^+$	$BF_3{\cdot}2ClCH_2COOH$[f] + $BF_3{\cdot}2CH_3COOH$	2–4	30	—	Me_3CCOOH(19) + C_9 acids (37) + C_{13} acids (24) + C_6 acids (10) + C_7 acids(10)	66	1719
Me_3COH	$Cu(CO)_3^+$	$BF_3{\cdot}2ClCH_2COOH$[f] + $BF_3{\cdot}2CH_3COOH$	2–4	30	Fe powder	Me_3CCOOH(19) + C_9 acids (41) + C_{13} acids (16) + C_6 acids (12) + C_7 acids (12)	70	1719
Me_3COH	$Cu(CO)_3^+$ + $Ag(CO)_2^+$	$BF_3{\cdot}2ClCH_2COOH$[f] + $BF_3{\cdot}2CH_3COOH$	2–4	30	—	Me_3CCOOH(18) + C_9 acids(40) + C_{13} acids(16) + C_7 acids(15) + C_6 acids(11)	81	1719
Me_3COH	$Cu(CO)_4^+$	BF_3–H_2O	2	25	—	Me_3CCOOH	94	1721, 1722

(continued)

TABLE 61. (*continued*)

Substrate	Active metal catalyst	Acid system	Reaction time (h)	Reaction temp. (°C)	Other conditions	Products (ratio)[a]	Yield (%)	Reference
EtCHOHMe	$Ag(CO)_2^+$	95% H_2SO_4	2–4	30	—	Me_3CCOOH(55) + C_9 acids (24) + $Et(Me)_2CCOOH$(21)	51	1719
Et_2CMeOH	$Ag(CO)_2^+$	BF_3–H_2O	2	25	—	$Et_2CMeCOOH$(79) + n-$C_3H_7CMe_2COOH$(16)	95	1721, 1722
n-$C_6H_{13}OH$	$Ag(CO)_2^+$	BF_3–H_2O	24	25	—	n-$C_3H_7CMe_2COOH$(12) + $Et_2CMeCOOH$(4)	16	1721, 1722
n-$C_4H_9CHOHMe$	$Ag(CO)_2^+$	BF_3–H_2O	2	25	—	n-$C_3H_7CMe_2COOH$(73) + $Et_2CMeCOOH$(23)	95	1721, 1722
n-$C_4H_9CHOHMe$	$Ag(CO)_2^+$	95% H_2SO_4	2–4	30	—	n-$C_3H_7CMe_2COOH$(43) + $Et_2CMeCOOH$(34)	88	1719
n-$C_8H_{17}OH$	$Ag(CO)_2^+$	BF_3–H_2O	168	25	—	n-$C_5H_{11}CMe_2COOH$(20) n-$C_4H_9CEtMeCOOH$(10) + $(n$-$C_3H_7)_2CMeCOOH$(5)	35	1721, 1722
n-$C_6H_{13}CHOHMe$	$Ag(CO)_2^+$	95% H_2SO_4	2–4	30	—	n-$C_4H_9CEtMeCOOH$(71) + n-$C_5H_{11}CMe_2COOH$(29)	79	1719
n-$C_6H_{13}CHOHMe$	$Ag(CO)_2^+$	$BF_3 \cdot H_2O$ + $BF_3 \cdot H_3PO_4$	2–4	30	—	n-$C_4H_9CEtMeCOOH$(73) + n-$C_5H_{11}CMe_2COOH$(27)	72	1719
n-$C_6H_{13}CHOHMe$	Fe powder	95% H_2SO_4	2–4	30	—	n-$C_4H_9CEtMeCOOH$(70) + n-$C_5H_{11}CMe_2COOH$(30)	36	1719
n-$C_6H_{13}CHOHMe$	Rh powder	$BF_3 \cdot H_2O$ + $BF_3 \cdot H_3PO_4$	2–4	30	—	C_9 acids(75) + C_7 acids(11)	28	1719
n-$C_6H_{13}CHOHMe$	$Cu(CO)_3^+$	95% H_2SO_4	2–4	30	—	C_9 acids (100)	90	1719
n-$C_6H_{13}CHOHMe$	$Cu(CO)_3^+$	$BF_3 \cdot 2ClCH_2COOH$[f] + $BF_3 \cdot 2CH_3COOH$	2–4	30	—	n-$C_4H_9CEtMeCOOH$(75) + n-$C_5H_{11}CMe_2COOH$(25)	10	1719
n-$C_6H_{13}CMe_2OH$	$Ag(CO)_2^+$	95% H_2SO_4	2–4	30	—	C_{10} acids (100)	61	1719
n-$C_6H_{13}CHOHC_3H_7$-n	$Ag(CO)_2^+$	95% H_2SO_4	2–4	30	—	C_{11} acids(100)	51	1719
1,5-Hexadiene	$Cu(CO)_4^+$	$BF_3 \cdot H_2O$	2	5–10	—	2-Ethyl-4-pentanolide	35	1721, 1722
1,7-Octadiene	$Ag(CO)_2^+$	$BF_3 \cdot H_2O$	2	20–30	—	2,2-Dimethyl-4-heptanolide + 1,4-dimethylcyclohexane-carboxylic acid	35 30	1721, 1722

1,9-Decadiene	$Cu(CO)_4^+$	$BF_3 \cdot H_2O$	2	6–10	—	2-Methyl-2-ethyl-4-octanolide + 2,2,7,7-tetramethyloctanedioic acid + 2-methyl-2-ethyloctanolide	40 30 20	1721, 1722,
1,12-Dodecanediol	$Cu(CO)_4^+$	$BF_3 \cdot H_2O$	3	20–30	—	No reaction	—	1721, 1722
1,12-Dodecanediol	$Cu(CO)_4^+$	$BF_3 \cdot H_2O$ + 98% H_2SO_4	3	20–25	—	2,2,9,9-Tetramethyldecanedioic acid + 1,4 and 1,5-lactones + 2-ethyl-2,8,8-trimethyldecanedioic acid	30 45 10	1721, 1722

[a] Acids produced in less than 10% yields are not reported in this table but are reported in the references.
[b] Ratio of 0.9:1 BF_3–H_2O to Cu_2O.
[c] Ratio of 0.7:1 BF_3–H_2O to Cu_2O.
[d] Ratio of 11.4:1 HF–H_2O to Cu_2O.
[e] Ratio of 6.8:1:0.9 HF–H_2O to BF_3 to Cu_2O.
[f] Ratio of 3:1 $BF_3 \cdot 2ClCH_2COOH$ to $BF_3 \cdot 2CH_3COOH$.

Hydrocarboxylation of aryl and benzyl halides using carbon monoxide and iron pentacarbonyl under phase transfer conditions which consist of aqueous sodium hydroxide, tetra(*n*-butyl)ammonium sulfate and either methylene chloride, benzene or toluene as the organic phase, produces[1723] the corresponding aromatic carboxylic acids (equation 791) in yields ranging from 7 to 75% (Table 62).

$$RX \xrightarrow[\text{aqueous phase: } H_2O,\ NaOH,\ (n\text{-}Bu_4N)_2SO_4]{\text{organic phase: CO, } Fe(CO)_5\text{, solvent}} RCOOH \qquad (791)$$

Another type of hydrocarboxylation reaction which takes place under phase transfer conditions is a bimetallic phase transfer catalyzed reaction[1724] (equation 792). Under the conditions of this reaction [1 atm. CO, 5M NaOH, benzene, dodecyltrimethylammonium chloride (DTAC), room temperature], hydrocarbonylation is only observed to occur if dicobalt octacarbonyl and triruthenium dodecacarbonyl are present in a 1:1 ratio, the reaction does not occur when either metal complex is used alone. Application of this procedure to monosubstituted acetylenes in methanol produces α-substituted γ-keto acids.

$$RC{\equiv}CH + MeI + CO(1\text{ atm}) \xrightarrow[\text{DTAC, 5M NaOH, } C_6H_6\text{, r.t}]{CO_2(CO)_8 + Ru_3(CO)_{12}(1:1)} \underset{\displaystyle \underset{\displaystyle COOH}{|}}{\overset{\displaystyle O}{\overset{\displaystyle \|}{R{-}CH{-}CH_2{-}C{-}Me}}}} \qquad (792)$$

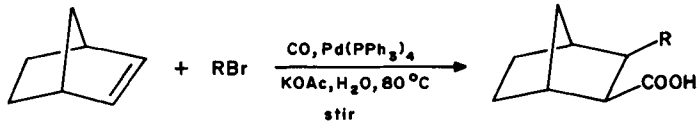
R = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-$EtOC_6H_4$, *c*-C_6H_{11}

Palladium, as the active element in a variety of compounds, has been used extensively in the recent literature to catalyze the hydrocarboxylation of hydrocarbons, aryl halides, olefins, olefinic dibromides and heteroatomic molecules, and has even been used to catalyze the insertion of carbon monoxide into the carbon–tellurium bond, to produce the corresponding carboxylic acids. A general reaction sequence which can be used to illustrate these reactions is shown in equation 793.

$$\text{substrate} + CO(\text{atm}) + \text{Pd catalyst} \xrightarrow[\text{conditions}]{\text{other}} \text{carboxylic acid product(s)} \qquad (793)$$

Table 63 reports the current literature information dealing with palladium catalyzed carbon monoxide additions which produce carboxylic acids.

One unusual report[1735] of the preparation of carboxylic acids involves the tetrakis (triphenylphosphine) palladium(0) catalyzed sequential insertion of bicyclo[2.2.1]hept-2-ene and carbon monoxide into Pd—C bonds (equation 794).



(794)

R=Ph, $PhCH_2$, $n\text{-}C_6H_{13}CH{=}{=}CH$, MeO_2CCH_2

The reaction is completely stereoselective, giving only the *cis,exo* product, and involves the initial formation of the Pd—C bond which undergoes insertion by reaction of the

TABLE 62. Iron and cobalt carbonyl catalyzed hydrocarbonylation reactions[1723]

RX	Medium	CO pressure (atm)	Ratio (cat./RX)	Reaction time (h)	Reaction temp. (°C)	Product	Yield (%)
PhBr	H_2O/C_6H_6	1	1/10	15	20	PhCOOH	75
PhBr	H_2O/CH_2Cl_2	1	1/10	3.5	20	PhCOOH	73
PhBr	H_2O/CH_2Cl_2	1	1/20	20	20	PhCOOH	69
PhBr	H_2O/CH_2Cl_2	60	1/50	27	25	PhCOOH	66
PhBr	MeOH	60	1/10	8	50	PhCOOH	7
$PhCH_2Cl$	H_2O/C_6H_5Me	60	1/10	29	50	$PhCH_2COOH$	61
m-$TolCH_2Br$	H_2O/CH_2Cl_2	1	1/10	24	25	*m*-$TolCH_2COOH$	54
m-$TolCH_2Cl$	H_2O/C_6H_5Me	60	1/10	47	60	*m*-$TolCH_2COOH$	31
o-$TolCH_2Br$	H_2O/CH_2Cl_2	1	1/10	24	25	*o*-$TolCH_2COOH$	69
m-$AnCH_2Cl$	H_2O/C_6H_5Me	60	1/10	51	50	*m*-$TolCH_2COOH$	35
p-$BrC_6H_4CH_2Br$	H_2O/CH_2Cl_2	1	1/10	24	25	*p*-$BrC_6H_4CH_2COOH$	50
m-$NCC_6H_4CH_2Br$	H_2O/CH_2Cl_2	60	1/10	21	25	*m*-$HOOCC_6H_4CH_2COOH$	43
2,4,6-$Me_3C_6H_2CH_2Cl$	H_2O/C_6H_5Me	60	1/10	26	60	2,4,6-$Me_3C_6H_2CH_2COOH$	37
2-$NaphCH_2Br$	H_2O/C_6H_5Me	60	1/10	53	60	2-$NaphCH_2COOH$	55
$PhCH_2Br$	H_2O/CH_2Cl_2	1	1/20[a]	40	20	$PhCH_2COOH$	9

[a]Catalyst used was $NaCo(CO)_4$.

TABLE 63. Palladium-catalyzed hydrocarboxylation reactions

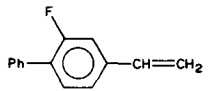
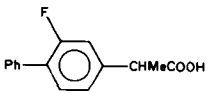
Substrate	Palladium catalyst	CO pressure (units)	Reaction time (h)	Reaction temp. (°C)	Other conditions	Products	Yield (%)	Reference
C_6H_6	$Pd(OAc)_2$	15 (atm)	20	100	Stir, autoclave	PhCOOH	26	1725
C_6H_5Me	$Pd(OAc)_2$	15 (atm)	20	100	Stir, autoclave	*p*-MeC_6H_4COOH +	18	1725
						o-MeC_6H_4COOH +	12	
						m-MeC_6H_4COOH	3	
C_6H_5OMe	$Pd(OAc)_2$	15 (atm)	20	100	Stir, autoclave	*p*-$MeOC_6H_4COOH$ +	43	1725
						o-$MeOC_6H_4COOH$	5	
Furan	$Pd(OAc)_2$	15 (atm)	20	100	Stir, autoclave	2-Furancarboxylic acid	35	1725
Thiophene	$Pd(OAc)_2$	15 (atm)	20	100	Stir, autoclave	2-Thiophenecarboxylic acid	18	1725
C_6H_5Cl	$Pd(OAc)_2$	15 (atm)	20	100	Stir, autoclave	*p*-ClC_6H_4COOH +	8	1725
						o-ClC_6H_4COOH +	4	
						m-ClC_6H_4COOH	2	
C_6H_5Br	$Pd(PPh_3)_2Cl_2$	30 (atm)	96	100	1) H_2O, Et_3N	PhCOOMe +	3	1726
					2) CH_2N_2	PhCOCOOMe	69.5	
C_6H_5I	$Pd(PPh_3)_2Cl_2$	150 (atm)	36	60	1) H_2O, Et_3N	PhCOOMe +	17.2	1726
					2) CH_2N_2	PhCOCOOMe	43.3	
C_6H_5I	$Pd(PPh_3)_2Cl_2$	150 (atm)	72	40	1) H_2O, Et_3N	PhCOOMe +	6.3	1726
					2) CH_2N_2	PhCOCOOMe	53.1	
p-TolI	$Pd(PPh_3)_2Cl_2$	150 (atm)	48	60	1) H_2O, Et_3N	*p*-TolCOOMe +	17.3	1726
					2) CH_2N_2	*p*-TolCOCOOMe	40.5	
2-Iodothiophene	$Pd(PPh_3)_2Cl_2$	150 (atm)	10	80	1) H_2O, Et_3N	2-ThiCOOMe +	24.1	1726
					2) CH_2N_2	2-ThiCOCOOMe	47.1	
p-BrC_6H_4Br	$Pd(PPh_3)_2Cl_2$	5 (atm)	4	95	30% aq. NaOH, *n*-Bu_4NI, *p*-Xylene	*p*-BrC_6H_4COOH	90	1727
$PhCH_2Cl$	$Pd(PPh_3)_2Cl_2$	5 (atm)	4	95	30% aq. NaOH, *n*-Bu_4NI, *p*-Xylene	$PhCH_2COOH$	83	1727
$PhCH_2Br$	$Pd(PPh_3)_4$	1 (atm)	6–10	25	CH_2Cl_2, $(C_6H_{13})_4\overset{+}{N}HSO_4^-$, aq. NaOH	$PhCH_2COOH$	84	1728
$PhCH_2Br$	$Pd(PPh_3)_4$	1 (atm)	6–10	25	CH_2Cl_2, aq. NaOH	$PhCH_2COOH$	57	1728
p-$TolCH_2Br$	$Pd(diphos)_2$[a]	1 (atm)	6–10	25	CH_2Cl_2, aq. NaOH	*p*-$TolCH_2COOH$	74	1728
o-$TolCH_2Cl$	$Pd(diphos)_2$[a]	1 (atm)	6–10	25	CH_2Cl_2, $(C_6H_{13})_4\overset{+}{N}HSO_4^-$, aq. NaOH	*o*-$TolCH_2COOCH_2$-C_6H_4Me-*o*	75	1728
o-$TolCH_2Cl$	$Pd(diphos)_2$[a]	1 (atm)	6–10	25	CH_2Cl_2, aq. NaOH	*o*-$TolCH_2COOH$	72	1728

o-TolCH$_2$Br	Pd(PPh$_3$)$_4$	1 (atm)	6–10	25	CH$_2$Cl$_2$, aq. NaOH, $(C_6H_{13})_4\overset{+}{N}HSO_4^-$	*o*-TolCH$_2$COOH	58	1728
o-TolCH$_2$Br	Pd(diphos)$_2$	1 (atm)	6–10	25	CH$_2$Cl$_2$, aq. NaOH, $(C_6H_{13})_4\overset{+}{N}HSO_4^-$	*o*-TolCH$_2$COOCH$_2$-C$_6$H$_4$Me-*o*	84	1728
o-TolCH$_2$Br	Pd(diphos)$_2$	1 (atm)	6–10	25	CH$_2$Cl$_2$, aq. NaOH	*o*-TolCH$_2$COOH	62	1728
p-FC$_6$H$_4$CH$_2$Br	Pd(PPh$_3$)$_4$	1 (atm)	6–10	25	CH$_2$Cl$_2$, aq. NaOH, $(C_6H_{13})_4\overset{+}{N}HSO_4^-$	*p*-FC$_6$H$_4$CH$_2$COOH	79	1728
2-NaphCH$_2$Br	Pd(PPh$_3$)$_4$	1 (atm)	6–10	25	CH$_2$Cl$_2$, aq. NaOH, $(C_6H_{13})_4\overset{+}{N}HSO_4^-$	2-NaphCH$_2$COOH	63	1728
2-NaphCH$_2$Br	Pd(PPh$_3$)$_4$	1 (atm)	6–10	25	C$_6$H$_6$, aq. NaOH, $(C_6H_{13})_4\overset{+}{N}HSO_4^-$	2-NaphCH$_2$COOH	84	1728
2-NaphCH$_2$Br	Pd(PPh$_3$)$_4$	1 (atm)	6–10	25	C$_6$H$_6$, aq. NaOH, $(C_6H_{13})_4\overset{+}{N}HSO_4^-$	2-NaphCH$_2$COOH	73	1728
2-NaphCH$_2$Br	Pd(dba)$_2$[b]	1 (atm)	6–10	25	CH$_2$Cl$_2$, aq. NaOH, $(C_6H_{13})_4\overset{+}{N}HSO_4^-$	2-NaphCH$_2$-COOCH$_2$Naph-2	15	1728
2-NaphCH$_2$Br	Pd(diphos)$_2$[a]	1 (atm)	6–10	25	CH$_2$Cl$_2$, aq. NaOH, $(C_6H_{13})_4\overset{+}{N}HSO_4^-$	2-NaphCH$_2$COOH	24	1728
2-NaphCH$_2$Br	Pd(diphos)$_2$[a]	1 (atm)	6–10	25	CH$_2$Cl$_2$, aq. NaOH	2-NaphCH$_2$COOH	85	1728
CH$_2$=CH$_2$	0.1% Pd/C	60 (atm)	6	170	HBr, EtCOOH	EtCOOH	98.4	1729
CH$_2$=CH$_2$	0.25% Pd/C	60 (atm)	4.5	170	HBr, EtCOOH	EtCOOH	96.8	1729
CH$_2$=CH$_2$	0.5% Pd/C	60 (atm)	4	170	HBr, EtCOOH	EtCOOH	96.4	1729
CH$_2$=CH$_2$	0.5% Pd/C	60 (atm)	2	170	HBr, MeCOOH	EtCOOH	95.6	1729
CH$_2$=CH$_2$	1% Pd/C	60 (atm)	3.5	170	HBr, EtCOOH	EtCOOH	95.3	1729
CH$_2$=CH$_2$	1.5% Pd/C	60 (atm)	3	170	HBr, EtCOOH	EtCOOH	96.7	1729
CH$_2$=CH$_2$	3.5% Pd/C	60 (atm)	3	170	HBr, EtCOOH	EtCOOH	96.4	1729
CH$_2$=CH$_2$	10% Pd/C	60 (atm)	3	170	HI, EtCOOH	EtCOOH	90.7	1729
MeCH=CH$_2$	5% Pd/C	100 (atm)	9	100	HI, MeCOOH	Me$_2$CHCOOH + MeCH$_2$CH$_2$COOH	54 46	1729
MeCH=CH$_2$	5% Pd/C	100 (atm)	6.5	120	HI, MeCOOH	Me$_2$CHCOOH + MeCH$_2$CH$_2$COOH	51 44.2	1729
MeCH=CH$_2$	5% Pd/C	100 (atm)	4	150	HI, MeCOOH	Me$_2$CHCOOH + MeCH$_2$CH$_2$COOH	50.4 42.0	1729
MeCH=CH$_2$	5% Pd/C	100 (atm)	2.5	200	HI, MeCOOH	Me$_2$CHCOOH + MeCH$_2$CH$_2$COOH	45 45	1729
MeCH=CH$_2$	5% Pd/C	100 (atm)	4	150	HI, EtCOOH	Me$_2$CHCOOH + MeCH$_2$CH$_2$COOH	46.7 46.7	1729
MeCH=CH$_2$	5% Pd/C	100 (atm)	5	150	*n*-C$_3$H$_7$I, MeCOOH	Me$_2$CHCOOH + MeCH$_2$CH$_2$COOH	53.4 39	1729
MeCH=CH$_2$	5% Pd/C	100 (atm)	5	150	*i*-C$_3$H$_7$I, MeCOOH	Me$_2$CHCOOH + MeCH$_2$CH$_2$COOH	41 36.1	1729

(*continued*)

TABLE 63. (*continued*)

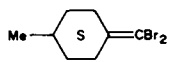
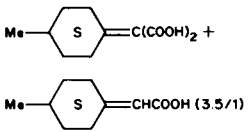
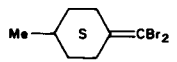
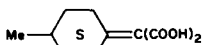
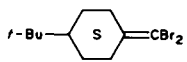
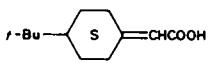
Substrate	Palladium catalyst	CO pressure (units)	Reaction time (h)	Reaction temp. (°C)	Other conditions	Products	Yield (%)	Reference
$MeCH{=}CH_2$	1% Pd/ 0.8% CaNaY	100 (atm)	5	150	HI, MeCOOH	$Me_2CHCOOH$ + $MeCH_2CH_2COOH$	47.4 36.5	1729
$MeCH{=}CH_2$	1% Pd/HM	100 (atm)	5	150	HI, MeCOOH	$Me_2CHCOOH$ + $MeCH_2CH_2COOH$	51.7 40.9	1729
$MeCH{=}CH_2$	$(CH_2)_2S(CH_2)_3OH$ | $Pd(OAc)_2$ on SiO_2	100 (atm)	2.5	150	HI, MeCOOH	$Me_2CHCOOH$ + $MeCH_2CH_2COOH$	36 26.3	1729
$MeCH{=}CH_2$	$Pd(OAc)_2$ on SiO_2	100 (atm)	2.5	150	HI, MeCOOH	$Me_2CHCOOH$ + $MeCH_2CH_2COOH$	40.1 32	1729
$Me_2CHCH{=}CHMe$	$PdCl_2$	1 (atm)	18	25	THF, $CuCl_2$, HCl, O_2	$Me_2CHCH_2CHMeCOOH$	84	23
n-$C_4H_9CH{=}CH_2$	5% Pd/C	25 (atm)	4.5	170	HI, MeCOOH	n-$C_4H_9CHMeCOOH$ + n-$C_6H_{13}COOH$	57.7 42.3	1729
n-$C_4H_9CH{=}CH_2$	5% Pd/C	50 (atm)	4	170	HI, MeCOOH	n-$C_4H_9CHMeCOOH$ + n-$C_6H_{13}COOH$	58.8 41.2	1729
n-$C_4H_9CH{=}CH_2$	5% Pd/C	60 (atm)	2.5	170	HI, MeCOOH	n-$C_4H_9CHMeCOOH$ + n-$C_6H_{13}COOH$	52.7 47.3	1729
n-$C_4H_9CH{=}CH_2$	5% Pd/C	85 (atm)	2	170	HI, MeCOOH	n-$C_4H_9CHMeCOOH$ + n-$C_6H_{13}COOH$	62.3 37.7	1729
n-$C_4H_9CH{=}CH_2$	5% Pd/C	120 (atm)	2	170	HI, MeCOOH	n-$C_4H_9CHMeCOOH$ + n-$C_6H_{13}COOH$	54.6	1729
n-$C_5H_{11}CH{=}CH_2$	$Pd(PPh_3)_2Cl_2$-$SnCl_2$(1:1)	[c]		—	Dioxane	n-$C_7H_{15}COOH$ + n-$C_5H_{11}CHMeCOOH$	82 14	1731
n-$C_3H_7CH{=}CHEt$ (*trans*)	$PdCl_2$	1 (atm)	18	25	THF, $CuCl_2$, HCl, O_2	n-$C_4H_9CHEtCOOH$ + $(n$-$C_3H_7)_2COOH$(1:1)	75	1730
n-$C_6H_{13}CH{=}CH_2$	$PdCl_2$	1 (atm)	18	25	THF, $CuCl_2$, HCl, O_2	n-$C_6H_{13}CHMeCOOH$	82	1730
n-$C_8H_{17}CH{=}CH_2$	$PdCl_2$	1 (atm)	4	25	THF, $CuCl_2$, HCl, O_2	n-$C_8H_{17}CHMeCOOH$	100	1730
n-$C_7H_{15}CH{=}CHMe$ (*cis*)	$PdCl_2$	1 (atm)	4	25	THF, $CuCl_2$, HCl, O_2	n-$C_8H_{17}CHMeCOOH$	59	1730
n-$C_7H_{15}CH{=}CHMe$ (*trans*)	$PdCl_2$	1 (atm)	4	25	THF, $CuCl_2$, HCl, O_2	n-$C_8H_{17}CHMeCOOH$	30	1730
n-$C_7H_{15}CH{=}CHMe$ (*trans*)	$PdCl_2$	1 (atm)	18	25	THF, $CuCl_2$, HCl, O_2	n-$C_8H_{17}CHMeCOOH$	77	1730

Cyclohexene	$Pd(PPh_3)_2Cl_2$	20–40 (kg/cm^2)	6	85	H_2O, acid, peroxide[d], dioxane	Cyclohexanecarboxylic Acid	—	1732
Cyclododecene	$PdCl_2$	1 (atm)	18	25	THF, $CuCl_2$, HCl, O_2	cyclododecanecarboxylic acid	64	1730
$CH_2{=}CH(CH_2)_4CH{=}CH_2$	$PdCl_2$	1 (atm)	18	25	THF, $CuCl_2$, HCl, O_2	$HOOCMeCH(CH_2)_4$-CHMeCOOH	93	1730
$CH_2{=}CH(CH_2)_6CH{=}CH_2$	$PdCl_2$	1 (atm)	19	25	THF, $CuCl_2$, HCl, O_2	$HOOCMeCH(CH_2)_6$-CHMeCOOH	100	1730
p-TolCH=CH_2	$PdCl_2$	1 (atm)	18	25	THF, $CuCl_2$, HCl, O_2	*p*-TolCHMeCOOH	58	1730
p-$Me_2CHCH_2C_6H_4$-CH=CH_2	$PdCl_2$	20 (kg/cm^2)	6	85	H_2O, acid, dioxane *m*-$ClC_6H_4CO_3H$	*p*-$Me_2CHCH_2C_6H_4$-CHMeCOOH	90.2	1732
p-$Me_2CHCH_2C_6H_4$-CH=CH_2	$PdCl_2$	20 (kg/cm^2)	6	85	H_2O, acid, dioxane	*p*-$Me_2CHCH_2C_6H_4$-CHMeCOOH	66.7	1732
	$PdCl_2$	20 (kg/cm^2)	6	85	H_2O, acid, peroxide[d], dioxane		—	1732
$PhTeC_6H_{13}$-*n*	$PdCl_2$–LiCl (1:2)	1 (atm)	20	25	1) MeCN 2) H_3O^+	PhCOOH	73	1733
Ph_2TeCl_2	$PdCl_2$–LiCl 2 × (1:2)	1 (atm)	20	25	1) MeCN 2) H_3O^+	PhCOOH	42	1733
Ph_2TeCl_2	$PdCl_2$–LiCl 2 × (1:2)	20 (atm)	20	25	1) MeCN 2) H_3O^+	PhCOOH	63	1733
$(p\text{-Ar})_2TeCl_2$	$PdCl_2$–LiCl 2 × (1:2)	1 (atm)	20	25	1) MeCN 2) H_3O^+	*p*-ArCOOH	36	1733
$(p\text{-An})_2TeCl_2$	$PdCl_2$–LiCl 2 × (1:2)	20 (atm)	20	25	1) MeCN 2) H_3O^+	*p*-AnCOOH	41	1733
RCH=CHHgCl (*cis*) R = *n*-Bu, Ph Me_3C, *n*-C_8H_{17}, *c*-C_6H_{11}, $(CH_2)_3CN$, $(CH_2)_8COOMe$	$PdCl_2$–LiCl				H_2O	RCH=CHCOOH (*cis*)	—	1734
PhCH=CHTePh (*cis*)	$PdCl_2$–LiCl (1:2)	1 (atm)	1.5	25	1) MeCN 2) H_3O^+	*cis*-PhCH=CHCOOH + *trans*-PhCH=CHCOOH + PhCOOH	32 52 8	1733
PhCH—CHTePh (*cis*)	$PdCl_2$–LiCl (1:2)	1 (atm)	20	25	1) MeCN 2) H_3O^+	*cis*-PhCH=CHCOOH + *trans*-PhCH—CHCOOH + PhCOOH	28 55 10	1733

(*continued*)

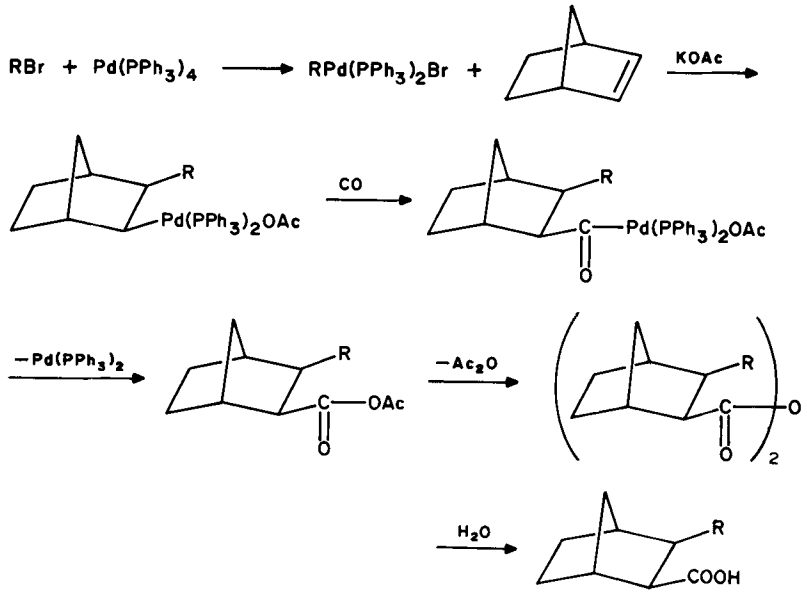
TABLE 63. (*continued*)

Substrate	Palladium catalyst	CO pressure (units)	Reaction time (h)	Reaction temp. (°C)	Other conditions	Products	Yield (%)	Reference
PhCH=CHTePh (*cis*)	$PdCl_2$–LiCl 2 × (1:2)	1 (atm)	20	25	1) MeCN 2) H_3O^+	*cis*-PhCH=CHCOOH + *trans*-PhCH=CHCOOH + PhCOOH	30 50 4.5	1733
PhCH=CHTePh (*cis*)	$PdCl_2$	1 (atm)	20	25	1) MeCN 2) H_3O^+	*cis*-PhCH=CHCOOH + *trans*-PhCH=CHCOOH + PhCOOH	3 60 4	1733
PhCH=CHTePh (*cis*)	$PdCl_2$–LiCl (1:2)	5 (atm)	1.5	25	1) MeCN 2) H_3O^+	*cis*-PhCH=CHCOOH + *trans*-PhCH=CHCOOH + PhCOOH	34 21 4	1733
PhCH=CHTePh (*cis*)	$PdCl_2$–LiCl (1:2)	20 (atm)	1.5	25	1) MeCN 2) H_3O^+	*cis*-PhCH=CHCOOH + *trans*-PhCH=CHCOOH + PhCOOH	46 22 5	1733
PhCH=CHTePh (*cis*)	$PdCl_2$–LiCl (1:2)	50 (atm)	1.5	25	1) MeCN 2) H_3O^+	*cis*-PhCH=CHCOOH + *trans*-PhCH=CHCOOH + PhCOOH	69 16 7	1733
EtCHMeCH=CBr_2	Pd (diphos)$_2$[a]	1 (atm)	40	70	Benzene, 5*N* NaOH, $PhCH_2\overset{+}{N}Et_3Cl^-$	EtCHMeCH=CHCOOH	64	1735
EtCHMeCH=CBr_2	Pd(diphos)$_2$	1 (atm)	42	50	*t*-$C_5H_{11}OH$, 5*N* NaOH, $PhCH_2\overset{+}{N}Et_3Cl^-$	EtCHMeCH=C(COOH)$_2$	82	1735
n-C_6H_{13}CH=CBr_2	Pd(diphos)$_2$	1 (atm)	70	70	Benzene, 5*N* NaOH, $PhCH_2\overset{+}{N}Et_3Cl$	*n*-C_6H_{13}CH=CHCOOH	55	1735
c-C_6H_{11}CH=CBr_2	Pd(diphos)$_2$	1 (atm)	43	70	Benzene, 5*N* NaOH, $PhCH_2\overset{+}{N}Et_3Cl^-$	*c*-C_6H_{11}CH=CHCOOH	6	1735
c-C_6H_{11}CH=CBr_2	Pd(diphos)$_2$	1 (atm)	42	50	*t*-$C_5H_{11}OH$, 5*N* NaOH, $PhCH_2\overset{+}{N}Et_3Cl^-$	*c*-C_6H_{11}CH=C(COOH)$_2$	32	1735

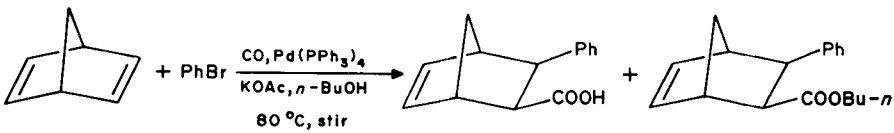
	$Pd(diphos)_2$	1 (atm)	22	70	Benzene, 5*N* NaOH, $PhCH_2\overset{+}{N}Et_3Cl^-$		33	1735
	$Pd(diphos)_2$	1 (atm)	40	50	*t*-$C_5H_{11}OH$, 5*N* NaOH, $PhCH_2\overset{+}{N}Et_3Cl^-$		28	1735
	$Pd(diphos)_2$	1 (atm)	29	75	Benzene, 5*N* NaOH, $PhCH_2\overset{+}{N}Et_3Cl^-$		84	1735
$PhCH{=}CBr_2$	$Pd(diphos)_2$	1 (atm)	19	50	*t*-$C_5H_{11}OH$, 5*N* NaOH, $PhCH_2\overset{+}{N}Et_3Cl^-$	$PhCH{=}C(COOH)_2$	93	1735
p-$AnCH{=}CBr_2$	$Pd(diphos)_2$	1 (atm)	22	50	*t*-$C_5H_{11}OH$, 5*N* NaOH, $PhCH_2\overset{+}{N}Et_3Cl^-$	*p*-$AnCH{=}C(COOH)_2$	87	1735
$Ph_2C{=}CBr_2$	$Pd(diphos)_2$	1 (atm)	20	50	*t*-$C_5H_{11}OH$, 5*N* NaOH, $PhCH_2\overset{+}{N}Et_3Cl^-$	$Ph_2C{=}CHCOOH$ + $Ph_2C{=}C(COOH)_2$ (1:6)	59	1735

[a] $Pd(diphos)_2$ is [1,2-bis(diphenylphosphino)ethane]palladium(0).
[b] $Pd(dba)_2$ is bis(dibenzylideneacetone)palladium(0).
[c] Synthesis gas made from CO and H_2O was used where $P_{CO} = PH_2 = 1$ atm.
[d] Peroxides used include hydrogen, benzoyl, cumyl or *m*-chloroperbenzoic acid peroxides.

$Pd(PPh_3)_4$ with vinyl, aryl, benzyl or alkyl bromides which contain an electron-withdrawing group in the α position. The mechanism for this reaction is illustrated in the scheme below.



Extension of this reaction[1736] to bicyclo[2.2.1]hepta-2,5-diene and bromobenzene in *n*-butanol produces both an acid and an ester (equation 795) resulting from the reaction of only one of the two double bonds in the strained olefin.



(795)

Another interesting preparation[1737] of carboxylic acids using a palladium-catalyzed hydrocarboxylation reaction involves the use of diazonium salts. By reaction of various diazonium salts and sodium acetate in acetonitrile at room temperature under 9 kg/cm^2 of carbon monoxide pressure with 2 mole percent of palladium acetate (equation 796), the corresponding carboxylic acids are produced in a convenient manner using mild conditions, albeit in only fair yields. The presence of both electron-withdrawing and donating substituents in the diazonium salt do not seem to materially affect the yield of the carboxylic acids produced.

Recently[1738–1741] rhodium, ruthenium and iridium compounds have all been reported to catalyze hydrocarboxylation type reactions with alcohols, olefins and lactones. With C_1 to C_{20} aliphatic alcohols, rhodium or ruthenium trichloride in the presence of iodide and Ti(IV) promoters at 150–250 °C. have been reported[1738] to react with hydrogen and carbon monoxide at 2000–10,000 psi to produce the corresponding homologous aliphatic carboxylic acids containing one more carbon atom than the starting alcohols. Rhodium and iridium trichlorides in the presence of an iodide promoter have also been reported[1739]

to produce dibasic (equation 797) and tribasic (equation 798) acids from diols and triols, respectively. Similar reactions occur with *p*-$HOCH_2C_6H_4C_6H_4CH_2OH$-*p* and *p*-$RCHOHC_6H_4CHOHR$.

$$ArN_2BF_4 + CO + NaOAc \xrightarrow[\text{1 h, room temp., stir; 2. aq. NaOH; 3. aq. HCl}]{\text{1. } Pd(OAc)_2,\ MeCN} ArCOOH \qquad (796)$$

Ar =	*p*-Tol	*m*-Tol	*o*-Tol	2,6-$Me_2C_6H_3$	*p*-An	*p*-ClC_6H_4
% Yield =	84	66	68	28	58	79

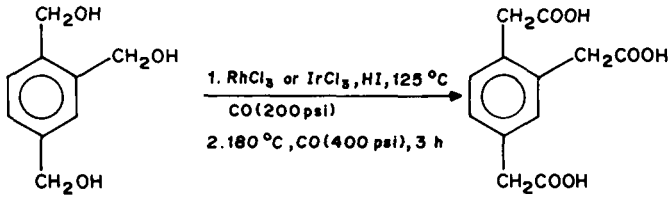
Ar =	*m*-ClC_6H_4	*o*-ClC_6H_4	*p*-BrC_6H_4	*p*-IC_6H_4	*o*-IC_6H_4	*p*-$O_2NC_6H_4$
% Yield =	78	82	84	74	74	65

α-naphthyl
72

Ar = 4′-benzo-15-crown-5[a]
Yield (%) = 28

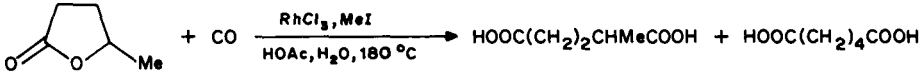
[a]The diazonium hexafluorophosphate was used.

$$p\text{-}HOCH_2C_6H_4CH_2OH \xrightarrow[\text{2. 180 °C, CO(400 psi), 3 h}]{\text{1. } RhCl_3 \text{ or } IrCl_3,\ HI,\ 125\,°C;\ CO(200\,psi)} p\text{-}HOOCCH_2C_6H_4CH_2COOH \qquad (797)$$



(798)

Rhodium trichloride in the presence of carbon monoxide, methyl iodide and water in a variety of solvents has also been reported[1740] to catalyze hydrocarboxylation of γ-valerolactone (equation 799, Table 64), while hydrocarboxylation of γ-alkyl-γ-lactones or



(799)

TABLE 64. Solvent effects on yields of dibasic acids from γ-valerolactone[1740]

Solvent	% Yield of 2-methylglutaric acid	% Yield of adipic acid
MeCOOH	5.3	8.0
EtCOOH	21.2	23.5
n-PrCOOH	27.7	31.8
n-$C_5H_{11}COOH$	32.2	33.7
n-$C_7H_{15}COOH$	43.2	40.9

δ-alkyl-δ-lactones using dirhodium tetracarbonyl dichloride and carbon monoxide in *n*-octanoic acid produces[1740] mixtures of *n*-dicarboxylic acids and isomers of 2-alkyldicarboxylic acids with poor selectivity.

In the presence of triruthenium dodecacarbonyl, olefins react[1741] with carbon monoxide at 500–4000 psi over a carbon bed at 200–400 °C in the presence of a promoter such as an alkyl halide (e.g. methyl iodide) or a heterocyclic aromatic amine (e.g. pyridine, 2- or 4-picoline, purine or 4-ethylpyridine) and a protonic coreactant (e.g. methyl alcohol) to produce (equation 800) a mixture of the corresponding monocarboxylic acids and esters.

$$\mathrm{MeCH{=}CH_2 + CO \xrightarrow[2000\,psi,\,122\,h]{MeI,\,MeOH,\,Ru_3(CO)_{12},\,255\,^\circ C}}$$
$$\mathrm{MeCH_2CO_2H + Me_2CHCO_2H + Me(CH_2)_2CO_2H} \quad (800)$$
$$\mathrm{+ Me_2CHCO_2CHMe_2 + Me(CH_2)_2CO_2CHMe_2}$$

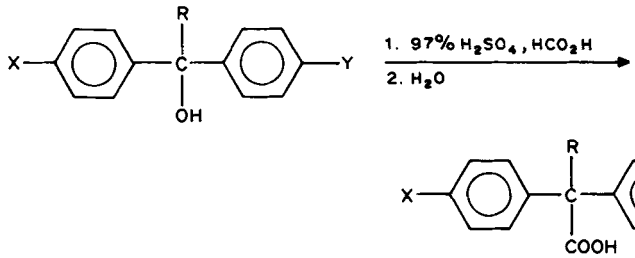
Ruthenium chloride complexed with di[1,2-bis(diphenylphosphino)ethane] has been reported[1742] to catalyze the hydrocarboxylation of methanol at 190 °C to afford a 95% yield of acetic acid.

Hydrocarboxylation-type reactions may also be accomplished in the absence of a metal catalyst using a variety of starting materials. Thus, if alkyl or cycloalkyl alcohols are treated (equation 801) with carbon monoxide at 100 atmospheres pressure and a complex of boron trifluoride with acetic, propionic or monochloroacetic acids in a 1:2 mole ratio at 25–150 °C, a mixture of the corresponding carboxylic acids is obtained[1743] (Table 65).

$$\text{alcohol} + \mathrm{CO\ (100\,atm)} \xrightarrow[\text{catalyst, heat}]{\mathrm{BF_3\ complex}} \text{acids} \quad (801)$$

Another example of this type of hydrocarboxylation reaction uncatalyzed by a metal catalyst is reported[1744] to occur when normal C_{20} to C_{24} alkenes are treated with carbon monoxide (500 to 2000 psi) and 92–98% sulfuric acid for 0.1 to 4 hours in an autoclave at 10 to 35 °C.

Sulfuric acid (97%) has also been used[1745] to catalyze the conversion of bis (4-halophenyl)methanols, 1,1-bis(4-halophenyl)ethanols and related alcohols into their corresponding 2,2-bis(4-halophenyl)acetic, -propionic and related acids (equation 802, Table 66). The carbon monoxide used in this conversion was generated *in situ* from formic acid, and it was observed that stirring had a profound effect on the yields of carboxylic acids realized.



(802)

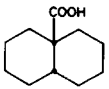
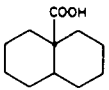
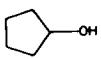
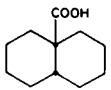
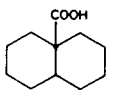
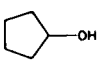
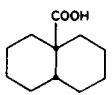
Sulfuric acid has also been used in a modification of the Koch–Haaf carboxylation reaction. This reaction, which usually involves the formation of tertiary carboxylic acids by treatment of alcohols with carbon monoxide in strong acid, has been used[1746] to produce diamantanedicarboxylic acids from hydroxydiamantanecarboxylic acids and

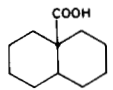
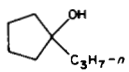
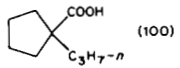
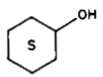
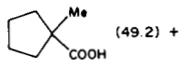
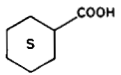
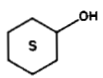
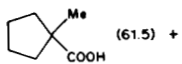
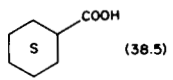
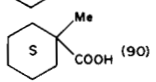
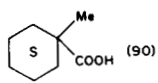
TABLE 65. BF_3 complex catalyzed acid formation from alcohols[1743]

Alcohol[a]	Catalyst	Temp. (°C)	Acid products (% yield)[b]	Overall yield (%)
t-BuOH	BF_3·2EtCOOH	80	Me_3CCOOH (62.7) + $Me_3CCH_2CMe_2COOH$ (13.6) + $Me_3CCH(i\text{-}Pr)COOH$ (12.3)	98.5
t-BuOH	BF_3·2MeCOOH	80	Me_3CCOOH (47.1) + $Me_3CCH_2CMe_2COOH$ (18.3) + $Me_3CH(i\text{-}Pr)COOH$ (16.3) + C_{13} acids (12.3)	81.1
t-BuOH	BF_3·2$ClCH_2COOH$/ BF_3·2MeCOOH (3:1)	70	Me_3CCOOH (64) + $Me_3CCH_2CMe_2COOH$ (16.1)	87.4
EtCHMeOH	BF_3·2$ClCH_2COOH$/ BF_3·2MeCOOH (3:1)	125	Me_3CCOOH (29.2) + EtCHMeCOOH (29.2) C_9 acids (41.6)	69.2
$EtCMe_2OH$	BF_3·2EtCOOH	90	Me_3CCOOH (23.5) + $EtCMe_2COOH$ (58.3) + $Et_2CMeCOOH$ (10.4)	94.7
$EtCMe_2OH$	BF_3·2MeCOOH	90	Me_3CCOOH (11.1) + $EtCMe_2COOH$ (55.5) + $Et_2CMeCOOH$ (12.4)	98.9
$EtCMe_2OH$	BF_3·2$ClCH_2COOH$/ BF_3·2MeCOOH (3:1)	80	Me_3CCOOH (14.8) + $EtCMe_2COOH$ (44.3) + $Et_2CMeCOOH$ (10.4) + C_9 acids (17.4)	96.5
$n\text{-}C_4H_9CHMeOH$	BF_3·2$ClCH_2COOH$/ BF_3·2MeCOOH (3:1)	100	$n\text{-}C_3H_7CMe_2COOH$ (36.8) + $Et_2CMeCOOH$ (46.2) + $n\text{-}C_3H_7CHEtCOOH$ (14.1)	91.3
$n\text{-}C_3H_7CMe_2OH$	BF_3·2MeCOOH	90	$n\text{-}C_3H_7CMe_2COOH$ (52.5) + $Et_2CHMeCOOH$ (24.6)	84.6
$n\text{-}C_5H_{11}CHMeOH$	BF_3·2$ClCH_2COOH$/ BF_3·2MeCOOH (3:1)	90	$n\text{-}C_5H_{11}CMe_2COOH$ (31.9) + $n\text{-}C_4H_9CMeEtCOOH$ (38.2) + $(n\text{-}C_3H_7)_2CMeCOOH$ (21.3)	85

(*continued*)

TABLE 65 (*continued*)

Alcohol[a]	Catalyst	Temp. (°C)	Acid products (% yield)[b]	Overall yield (%)
$(n\text{-}C_3H_7)_2CHOH$	$BF_3 \cdot 2ClCH_2COOH$/ $BF_3 \cdot 2MeCOOH$ (3:1)	90	$n\text{-}C_5H_{11}CMe_2COOH$ (39.0) + $n\text{-}C_4H_9CMeEtCOOH$ (36.0) + $(n\text{-}C_3H_7)_2CMeCOOH$ (13.8)	82
$n\text{-}C_6H_{13}CHMeOH$	$BF_3 \cdot 2ClCH_2COOH$/ $BF_3 \cdot 2MeCOOH$ (3:1)	90	$n\text{-}C_5H_{11}CMe_2COOH$ (34.2) + $n\text{-}C_4H_9CMeEtCOOH$ (43.6) + $(n\text{-}C_3H_7)_2CMeCOOH$ (11.1)	89.6
	$BF_3 \cdot 2EtCOOH$	80	 (72) +  (16) + unidentified decalinecarboxylic acids (12)	50
	$BF_3 \cdot 2MeCOOH$	90	 (60) +  (29.5) + unidentified decalinecarboxylic acids (10.5)	55.7
	$BF_3 \cdot 2ClCH_2COOH$/ $BF_3 \cdot 2MeCOOH$ (3:1)	90	 (18.5) +	76

			 (47.6)	
	$BF_3 \cdot 2ClCH_2COOH$/ $BF_3 \cdot 2MeCOOH$ (3:1)	90	 (100)	66
	$BF_3 \cdot 2MeCOOH$	90	 (49.2) +  (50.8)	54.5
	$BF_3 \cdot 2ClCH_2COOH$/ $BF_3 \cdot 2MeCOOH$ (3:1)	80	 (61.5) +  (38.5)	69.5
	$BF_3 \cdot 2MeCOOH$	90	 (90)	63.7
	$BF_3 \cdot 2ClCH_2COOH$/ $BF_3 \cdot 2MeCOOH$ (3:1)	90	 (90)	62.7

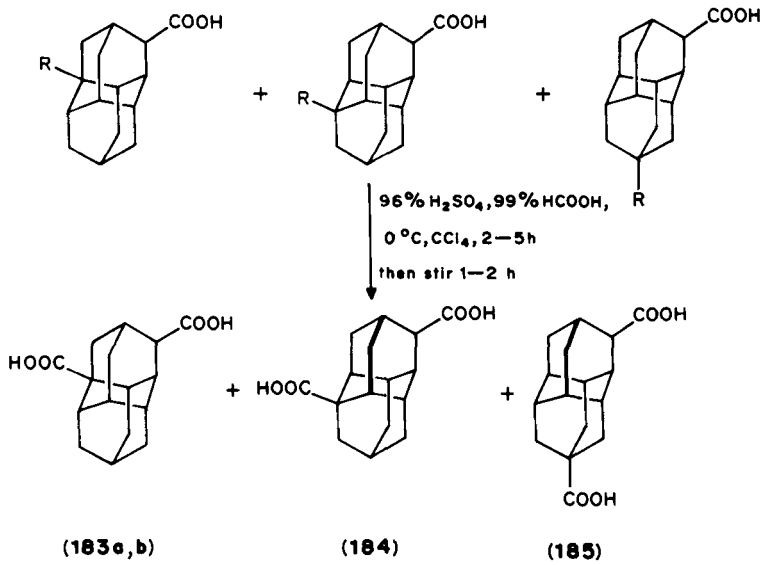
[a] Mole ratio catalyst: alcohols = 2:1.
[b] Other acids produced in < 10% yield are also reported by the authors but are not included in this table. See original reference for further information.

TABLE 66. Sulfuric acid catalyzed hydrocarboxylation of bis(4-halophenyl)methanols and ethanols

R[a]	X[a]	Y[a]	Stirring conditions	Rx time (h)	Rx temp. (°C)	Acid product yield (%)
H	Cl	Cl	Vigorous[a]	1.3	15–16	2
H	Cl	Cl	No	1.3	15–16	92
Me	Cl	Cl	No	1.3	15–16	16
Me	Cl	Cl	No	10.2	20–21	85
H	F	F	No	2.1	15–16	95
H	F	Br	No	2.1	15–16	94
H	Br	Br	No	2.1	14–16	76
H	I	I	No	2.1	14–16	14
Me	H	H	No	10.1	14–16	60
Me	F	F	No	10.1	20–21	60
Me	F	Cl	No	10.1	20–21	72

[a]See equation (802).
[b]Stirring speed ~ 1000 rpm.

bromodiamantanecarboxylic acids (equation 803) by utilizing formic acid instead of carbon monoxide.



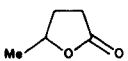
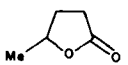
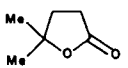
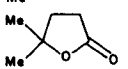
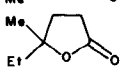
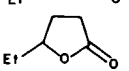
(803)

R = OH, overall yield 96% with distribution 7.5% (**183a**), 5.5% (**183b**), 22.6% (**184**) and 64.4% (**185**)

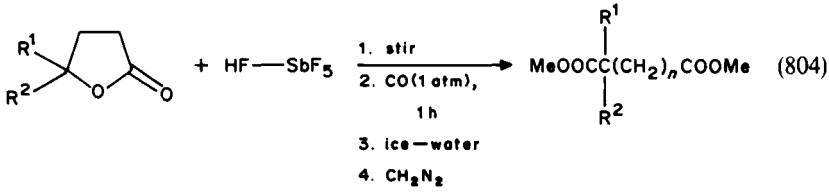
R = Br, overall yield 80% with distribution 18.6% (**183a**), 14.9% (**183b**), 62.6% (**184**) and 4.9% (**185**)

An example of a proton acid–Lewis acid mixture ($HF–SbF_5$) used to catalyze the hydrocarboxylation of γ-butyrolactones to produce (equation 804) the corresponding dicarboxylic acids in good yields has been reported[1747] (Table 67). The dicarboxylic acid

TABLE 67. Hydrocarboxylation of γ-butyrolactones[1747]

Lactones	Rx temp. (°C)	Mole ratio SbF_5/lactone	Mole ratio HF/SbF_5	Product	Yield (%)
	30	6.1	1.7	$MeOOCCHMeCH_2COOMe$	32
	30	5.0	2.3	$MeOOCCHMe(CH_2)_2COOMe$	100
	0	4.9	2.2	$MeOOCCHMe(CH_2)_2COOMe$	100
	0	4.9	2.5	$MeOOCCMe_2(CH_2)_2COOMe$	100
	0	2.9	5.5	$MeOOCCMe_2(CH_2)_2COOMe$	100
	−20	2.9	5.3	$MeOOCCMe_2(CH_2)_2COOMe$	100
	0	5.0	5.5	$MeOOCCHMe(CH_2)_3COOMe$	96

products were isolated as their dimethyl esters by reaction with diazomethane. A proposed mechanism is reported to justify the results obtained.



(804)

Finally, treatment of organoboranes with ^{13}C labelled carbon monoxide at 1 atmosphere pressure followed by oxidation using hydrogen peroxide resulted[1748] in the preparation (equation 805) of excellent yields of ^{13}C labelled carboxylic acids (Table 68).

$$RCH{=}CH_2 \xrightarrow[3.\ H_2O_2,\ NaOAc\quad 4.\ AgNO_3,\ NaOH,\ 50\,^{\circ}C,\ 30\ min]{1.\ R_2BH(9\text{-}BBN),\ THF\quad 2.\ ^{13}CO,\ KBH(OPr\text{-}i)_2} RCH_2CH_2COOH \qquad (805)$$

BBN = alkylborabicyclo[3.3.1]nonane

*E. Acids by Carbonation of Organometallic Reagents

Examples of the reaction of organometallic reagents with carbon dioxide to prepare carboxylic acids which are reported in the recent literature, again demonstrate that Grignard reagents and organolithium reagents are the most frequently employed organometallic reagents.

Grignard reagents prepared from a variety of organic halides or substrates containing an active hydrogen have been carbonated (equation 806) by treatment with solid or gaseous carbon dioxide to produce the corresponding carboxylic acids in good to excellent yields (Table 69).

$$RMgX + CO_2(s \text{ or } g) \xrightarrow[2.\ H_3O^+]{1.\ \text{reaction conditions}} RCOOH \qquad (806)$$

In addition to the 'normal' Grignard carbonation reactions presented in Table 69, two publications[1756,1757] have reported that heterocyclic magnesium halide carbon dioxide complexes can be used as carbon dioxide carriers when allowed to react with substrates possessing an active hydrogen atom such as ketones containing α-protons. The general

TABLE 68. Hydrocarboxylation of organoboranes[1748]

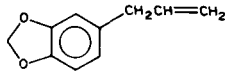
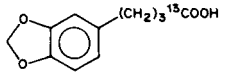
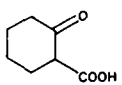
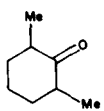
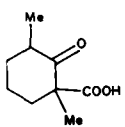
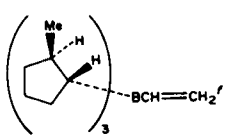
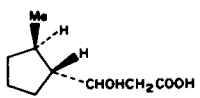
Alkene	Product	Yield (%)
$Me(CH_2)_6CH{=}CH_2$	$Me(CH_2)_8\,^{13}COOH$	94
$HO(CH_2)_9CH{=}CH_2$	$HO(CH_2)_{11}\,^{13}COOH$	94
p-$TolSCH_2CMe{=}CH_2$	*p*-$TolSCH_2CHMeCH_2\,^{13}COOH$	89
		93
		84

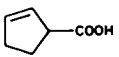
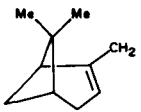
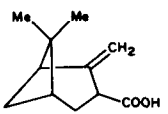
TABLE 69. Preparation of carboxylic acids by carbonation of Grignard reagents RMgX

R	X	CO_2 g(pressure) or s	Conditions	Products	Yield (%)	Reference
$MeCH_2CHMe$	Br	$Fe(CO)_5$[a]	1) THF 2) I_2, H_2O	$MeCH_2CHMeCOOH$	15	1749
$Me(CH_2)_3$	Cl	$^{14}CO_2$(g)[b]	Room temp., 15 h[c]	$Me(CH_2)_3\,^{14}COOH$	32	1750
				+ $[Me(CH_2)_3]_2\,^{14}CO$	24	
				+ $[Me(CH_2)_3]_3\,^{14}COH$	12	
Me_3C	Cl	$^{14}CO_2$ (g)[b]	Room temp., 15 h[c]	$Me_3C^{14}COOH$	76	1750
$Me(CH_2)_5$	Br	$Fe(CO)_5$[a]	1) THF 2) I_2, H_2O	$Me(CH_2)_5COOH$	60	1749
$Me(CH_2)_7$	Br	$Fe(CO)_5$[a]	1) THF 2) I_2, H_2O	$Me(CH_2)_7COOH$	65	1749
c-C_6H_{11}	Br	$Fe(CO)_5$[a]	1) THF 2) I_2, H_2O	c-$C_6H_{11}COOH$	30	1749
$MeOCH_2$	Cl	$^{14}CO_2$(g)[b]	Room temp., 15 h[c]	$MeOCH_2\,^{14}COOH$	1	1750
				+ $(MeOCH_2)_2\,^{14}CO$	89.5	
				+ $(MeOCH_2)_3COOH$	< 5	
$MeO(CH_2)_2$	Cl	$^{14}CO_2$(g)[b]	Room temp., 15 h[c]	*d*	—	1750
$MeO(CH_3)_3$	Cl	$^{14}CO_2$(g)[b]	Room temp., 15 h[c]	$MeO(CH_2)_3\,^{14}COOH$	33	1750
				+ $[MeO(CH_2)_3]_2\,^{14}CO$	45	
				+ $[MeO(CH_2)_3]_3\,^{14}COH$	14	
$(MeCH_2)_2CO$	—	g(5 kg/cm^2)	'MgI$_2$', Et_3N, MeCN, 3 h, 25 °C[e]	$MeCH_2COCHMeCOOH$	58	1751
$[Me(CH_2)_2]_2CO$	—	g(5 kg/cm^2)	'MgI$_2$', Et_3N, MeCN, 3 h, 25 °C[e]	$Me(CH_2)_2COCHEtCOOH$	75	1751
$(Me_2CH)_2CO$	—	g(5 kg/cm^2)	'MgI$_2$', Et_3N, MeCN, 3 h, 25 °C[e]	$Me_2CHCOCMe_2COOH$	65	1751
	—	g(5 kg/cm^2)	'MgI$_2$', Et_3N, MeCN, 3 h, 25 °C[e]		35	1751
	—	g(5 kg/cm^2)	'MgI$_2$', Et_3N, MeCN, 3 h, 25 °C[e]		70	1751
	—	g(5 kg/cm^2)	'MgI$_2$', Et_3N, MeCN, 3 h, 25 °C[e]		65	1751

(*continued*)

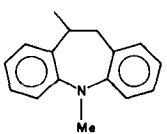
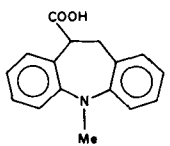
TABLE 69 (*continued*)

R	X	CO_2 g(pressure) or s	Conditions	Products	Yield (%)	Reference
$(n\text{-}C_6H_{13})_3BCH{=}CH_2$[f]	Cl	g(25 kg/cm^2)	1) THF, 1 h, 0 °C 2) NaOH, 30% H_2O_2, 40 °C, stir 4 h 3) 6 *M* HCl (pH = 6)	$n\text{-}C_6H_{13}CHOHCH_2COOH$	82	1752
$(n\text{-}C_7H_{15})_3BCH{=}CH_2$[f]	Cl	g(25 kg/cm^2)	1) THF, 1 h, 0° 2) NaOH, 30% H_2O_2, 40 °C, stir 4 h 3) 6 *M* HCl (pH = 6)	$n\text{-}C_7H_{15}CHOHCH_2COOH$	81	1752
$(n\text{-}C_8H_{17})_3BCH{=}CH_2$[f]	Cl	g(25 kg/cm^2)	1) THF, 1 h, 0 °C 2) NaOH, 30% H_2O_2, 40 °C, stir 4 h 3) 6 *M* HCl (pH = 6)	$n\text{-}C_8H_{17}CHOHCH_2COOH$	85	1752
$(n\text{-}C_{10}H_{21})_3BCH{=}CH_2$[f]	Cl	g(25 kg/cm^2)	1) THF, 1 h, 0 °C 2) NaOH, 30% H_2O_2, 40 °C, stir 4 h 3) 6 *M* HCl (pH = 6)	$n\text{-}C_{10}H_{21}CHOHCH_2COOH$	78	1752
$(n\text{-}C_{12}H_{25})_3BCH{=}CH_2$[f]	Cl	g(25 kg/cm^2)	1) THF, 1 h, 0 °C 2) NaOH, 30% H_2O_2, 40 °C, stir 4 h 3) 6 *M* HCl (pH = 6)	$n\text{-}C_{12}H_{25}CHOHCH_2COOH$	83	1752
$(c\text{-}C_6H_{11})_3BCH{=}CH_2$[f]	Cl	g(25 kg/cm^2)	1) THF, 1 h, 0 °C 2) NaOH, 30% H_2O_2, 40 °C, stir 4 h 3) 6 *M* HCl (pH = 6)	$c\text{-}C_6H_{11}CHOHCH_2COOH$	74	1752
 (*trans*)	Cl	g(25 kg/cm^2)	1) THF, 1 h, 0 °C 2) NaOH, 30% H_2O_2, 40 °C, stir 4 h 3) 6 *M* HCl (pH = 6)	 (*trans*)	80	1752

$CH_2{=}CHCH_2$	Br[g]	g(1 atm)	1) THF, 0.5 h at −70 °C then warm to 0 °C 2) NH_4Cl, NaOH 3) H_3O^+	$CH_2{=}CHCH_2COOH$	75	1753
$CH_2{=}CMeCH_2$	Cl[g]	g(1 atm)	1) THF, 0.5 h at −70 °C then warm to 0 °C 2) NH_4Cl, NaOH 3) H_3O^+	$CH_2{=}CMeCH_2COOH$	92	1753
$CH_2{=}CPhCH_2$	Cl[g]	g(1 atm)	1) THF, 0.5 h at −70 °C then warm to 0 °C 2) NH_4Cl, NaOH 3) H_3O^+	$CH_2{=}CPhCH_2COOH$	76	1753
$MeCH{=}CHCH_2$	Cl[g]	g(1 atm)	1) THF, 0.5 h at 70 °C then warm to 0 °C 2) NH_4Cl, NaOH 3) H_3O^+	$MeCH{=}CHCH_2COOH$	94	1753
	Cl[g]	g(1 atm)	1) THF, 0.5 h at −70 °C then warm to 0 °C 2) NH_4Cl, NaOH 3) H_3O^+		89	1753
	Cl	g(1 atm)	1) THF, 0.5 h at −70 °C then warm to 0 °C 2) NH_4Cl, NaOH 3) H_3O^+		96	1753
$PhCH_2$	Cl	$^{14}CO_2$(g)[b]	Room temp, 15 h[c]	$PhCH_2{}^{14}COOH$	98	1750
$PhCH_2OCH_2$	Cl	$^{14}CO_2$(g)[b]	Room temp, 15 h[c]	$PhCH_2OCH_2{}^{14}COOH$ + $(PhCH_2OCH_2)_2{}^{14}CO$ + $(PhCH_2OCH_2)_3{}^{14}COH$	< 2 89 < 5	1750
$PhCH_2SCH_2$	Cl	$^{14}CO_2$(g)[b]	Room temp, 15 h[c]	$PhCH_2SCH_2{}^{14}COOH$	70	1750
PhCOMe	—	g(5 kg/cm^2)	'MgI$_2$', Et_3N, MeCN, 3 h, 25 °C[e]	$PhCOCH_2COOH$	75	1751
$PhCOCH_2Me$	—	g(5 kg/cm^2)	'MgI$_2$', Et_3N, MeCN, 3 h, 25 °C[e]	PhCOCHMeCOOH	85	1751

(*continued*)

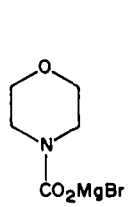
TABLE 69 (*continued*)

R	X	CO_2 g(pressure) or s	Conditions	Products	Yield (%)	Reference
$PhCOCHMe_2$	—	g(5 kg/cm²)	'MgI_2', Et_3N, MeCN, 3 h, 25 °C[e]	$PhCOCMe_2COOH$	90	1751
Ph	Br	$Fe(CO)_5$[a]	1) THF 2) I_2, H_2O	PhCOOH	70	1749
Ph	Br	$^{14}CO_2$(g)[b]	Room temp., 15 h[c]	Ph ^{14}COOH	44	1750
				+ Ph_2 ^{14}CO	12	
p-Tol	Br	$Fe(CO)_5$[a]	1) THF 2) I_2, H_2O	*p*-TolCOOH	78	1749
p-An	Br	$Fe(CO)_5$[a]	1) THF 2) I_2, H_2O	*p*-AnCOOH	59	1749
p-An	Br	$^{14}CO_2$(g)[b]	Room temp., 15 h[c]	*p*-An ^{14}COOH	73	1750
				+ *p*-An_2 ^{14}CO	8.4	
				+ *p*-An_3 ^{14}COH	2	
o-An	Br	$^{14}CO_2$(g)[b]	Room temp., 15 h[c]	*o*-An ^{14}COOH	7	1750
				+ *o*-An_2 ^{14}CO	89	
				+ *o*-An_3COH	1.6	
p-$F_3C(CH_2)_3C_6H_4$	Br	s	Ether, room temp. 4–5 h	*p*-$F_3C(CH_2)_3C_6H_4COOH$	50	1754
	Br	s	THF, −20 °C		50–60	1755

[a] Produces the complex $[RCOFe(CO)_4]^-MgBr^+$ initially which is cleaved to the acid by treatment with I_2 and H_2O.
[b] Generated from $Ba^{14}CO_3$ upon treatment with H_2SO_4.
[c] Reaction is performed via what the author[1750] calls the 'ketone route' which is an excess of Grignard reagent over carbon dioxide (3:1), elevated temperature (room temperature) and extended reaction time (15 hours).
[d] Grignard reagent did not form.
[e] 'MgI_2' formed by reaction of $MgCl_2$ with NaI. Ratio of ketone: MgI_2: Et_3N = 1:2:4.
[f] Grignard reagent is $(R_3BCH{=}CH_2)MgCl$; intermediate is $R_2BCHRCH_2CO_2MgCl$.
[g] Grignard reagent is prepared by evaporating Mg into THF cooled to −110 °C and then adding the allyl halide.

reaction which may be used to illustrate this transcarboxylation reaction is shown in equation 807, and involves the reaction of heterocyclic magnesium halide complex with gaseous carbon dioxide to produce the carbon dioxide carrier, which upon reaction with an enolizable ketone affords the reduced complex and the corresponding β-keto acid. The heterocyclic magnesium halide or lithium carbon dioxide complexes studied (**A–I**) are shown below and the results obtained using them are reported in Table 70.

$$\text{Complex MgBr} \xrightarrow{CO_2(g)} \text{Complex } CO_2MgBr + RCOCH_2R' \xrightarrow[2.\ H_3O^+]{1.\ DMF,\ Ar,\ stir,\ 25\,^\circ C} \text{Complex H} + RCOCHR'COOH \qquad (807)$$



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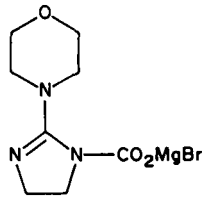

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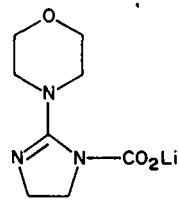

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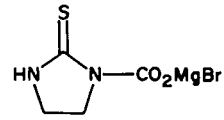

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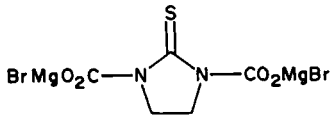
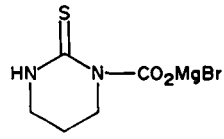
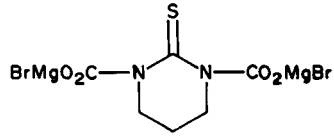


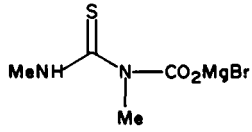
(E)



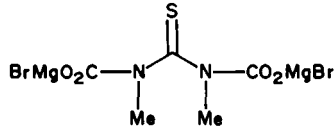
(F)



(G)



(H)



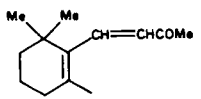
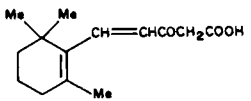
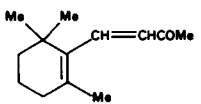
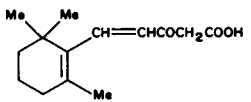
(I)

As previously mentioned, carbonation of organolithium reagents remains a frequently utilized approach to the synthesis of carboxylic acids. In addition to lithium alkylates and arylates, enolates, vinylates, aluminates, borates and phosphorates have all been recently reported to undergo carbonation with solid or gaseous carbon dioxide. The general sequence for these reactions is illustrated in equation 808, and the results obtained with various substrates are reported in Table 71.

$$RX(H) + R'Li \xrightarrow[\text{conditions}]{\text{reaction}} RLi \xrightarrow[2.\ H_3O+]{1.\ CO_2\ (s\ or\ g)\ \text{reaction}} RCOOH \qquad (808)$$

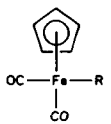
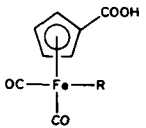
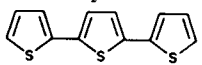
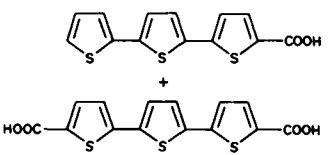
One report[1775] of the carboxylation of organoaluminum compounds to produce

TABLE 70. Preparation of carboxylic acids via transcarboxylation reactions

Ketone[a]	Time (h)	β-Keto acid Product	% Yield using carrier[c] A	B	C	D	E	F	G	H	I	Reference
PhCOMe	20	$PhCOCH_2COOH$	—	—	—	34	74	31	79	5	52	1757
PhCOMe	40	$PhCOCH_2COOH$	NR	50	9	—	—	—	—	—	—	1756
PhCOMe	19[b]	$PhCOCH_2COOH$	—	58	—	—	—	—	—	—	—	1756
$PhCOCH_2Me$	20	PhCOCHMeCOOH	—	—	—	2	49	2	80	3	12	1757
PhCH=CHCOMe	19[b]	$PhCH{=}CHCOCH_2COOH$	—	76	—	—	—	—	—	—	—	1756
PhCH=CHCOMe	40	$PhCH{=}CHCOCH_2COOH$	—	51	—	—	—	—	—	—	—	1756
PhCH=CHCOMe	20	$PhCH{=}CHCOCH_2COOH$	—	—	—	25	78	11	78	5	71	1757
$PhCH_2SCOMe$	65[b]	$PhCH_2SCOCH_2COOH$	—	54	—	—	—	—	—	—	—	1756
	19[b]		—	77	—	—	—	—	—	—	—	1756
	20		—	—	—	19	58	21	53	2	39	1757

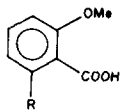
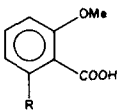
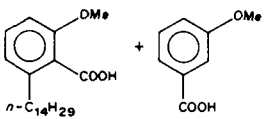
[a] Molar ratio of complex carrier to ketone = 4:1.
[b] Reaction was run under a continuous stream of CO_2 at 3 kg/cm^2.
[c] See text for structure of complexes A–I used.

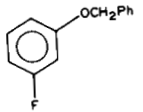
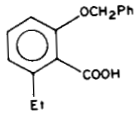
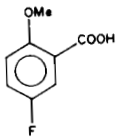
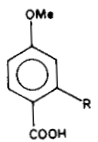
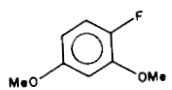
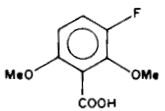
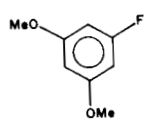
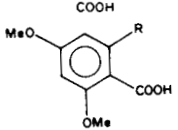
TABLE 71. Preparation of carboxylic acids by carbonation of lithium reagents

Substrate	Reaction conditions for lithium reagent preparation	CO_2 g(units) or s	Reaction conditions for carbonation reaction	Product	Yield (%)	Reference
						
	n-BuLi, THF, hexane −78 °C, stir	s	Stir 1–1.5 h, −78 °C increasing to 25 °C			1758
R = Ph R = η^5-$C_5H_4Mn(CO)_3$ R = $PhCH_2$					63 53 67	
						
	$(i\text{-Pr})_2NLi$, *n*-BuLi, THF, hexane, −78 °C stir 1 h	s	Stir 2 h, −78 °C increasing to 25 °C with stirring overnight			1759
	0.5 eq. $(i\text{-Pr})_2NLi$			Monoacid + diacid	68.5 3	
	1 eq. $(i\text{-Pr})_2NLi$			Monoacid + diacid	21 33	
	2 eq. $(i\text{-Pr})_2NLi$			Monoacid + diacid	0 90	

(continued)

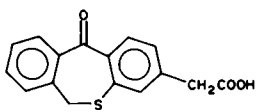
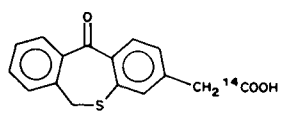
TABLE 71. (*continued*)

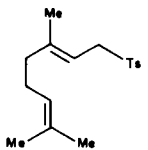
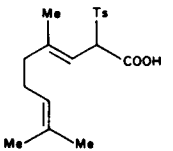
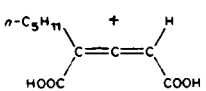
Substrate	Reaction conditions for lithium reagent preparation	CO_2 g(units) or s	Reaction conditions for carbonation reaction	Product	Yield (%)	Reference
o-AnF	RLi, ether, 0 °C rising to 25 °C over 1 h	s	Stir			1760
	R = Me			R = Me	6	
	R = Et			R = Et	29	
	R = *n*-Pr			R = *n*-Pr	40.1	
	R = *i*-Pr			R = *i*-Pr	0	
	R = *n*-Bu			R = *n*-Bu	16	
	R = *n*-$C_{12}H_{25}$			R = *n*-$C_{12}H_{25}$	28	
	R = *n*-$C_{14}H_{29}$			R = *n*-$C_{14}H_{29}$	39	
	R = *n*-$C_{15}H_{31}$			R = *n*-$C_{15}H_{31}$	35	
o-AnBr	*n*-BuLi, ether, 0 °C; reflux 1 h	s	Stir	*o*-AnCOOH	35.8	1760
m-AnF	RLi, ether, 0 °C rising to 25 °C over 1 h	s	Stir			1760
	R = Me			R = Me	7	
	R = Et			R = Et	54	
	R = *n*-Pr			R = *n*-Pr	84	
	R = *i*-Pr			R = *i*-Pr	0	
	R = *n*-Bu			R = *n*-Bu	25	
	R = *n*-$C_{12}H_{25}$			R = *n*-$C_{12}H_{25}$	29	
	R = *n*-$C_{14}H_{29}$			R = *n*-$C_{14}H_{29}$	37	
	R = *n*-$C_{15}H_{31}$			R = *n*-$C_{15}H_{31}$	41	
m-AnBr	*n*-$C_{14}H_{29}Li$, ether, 0 °C to −10 °C, stir 2 h	s	Stir		—	1760

	EtLi, ether, 0 °C, stir	s	Stir		31	1760
p-AnF	*n*-BuLi, ether, 0 °C rising to 25 °C over 1 h	s	Stir		—	1760
p-AnF	RLi, ether, 0 °C rising to 25 °C over 1 h	s	Stir			1760
	R = *n*-$C_{12}H_{25}$ R = *n*-$C_{15}H_{31}$			R = *n*-$C_{12}H_{25}$ R = *n*-$C_{15}H_{31}$	17 42.5	
	EtLi, ether, stir 0 °C rising to 25 °C over 2 h	s	Stir		40	1761
	RLi, ether, stir 0 °C rising to 25 °C over 2 h	s	Stir			1761
	R = Me R = Et R = *n*-Pr R = *n*-C_5H_{11} R = *n*-C_7H_{15} R = *n*-$C_{15}H_{31}$			R = Me R = Et R = *n*-Pr R = *n*-C_5H_{11} R = *n*-C_7H_{15} R = *n*-$C_{15}H_{31}$	15 45 — 37 39 34	

(*continued*)

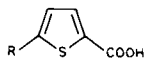
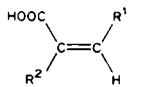
TABLE 71 (*continued*)

Substrate	Reaction conditions for lithium reagent preparation	CO_2 g(units) or s	Reaction conditions for carbonation reaction	Product	Yield (%)	Reference
$R^1R^2C(OH)CH_2Cl$	1) *n*-BuLi, ether, THF, −78 °C, Ar 2) $C_{10}H_8Li$, THF, −78 °C, stir 5 h	s	Stir overnight	$R^1R^2C(OH)CH_2COOH$		1762
R^1 R^2				R^1 R^2		
H Ph				H Ph	22[a]	
Me MeCH=CH				Me MeCH=CH	46[a]	
MeCH=CH MeCH=CH				MeCH=CH MeCH=CH	64[a]	
MeCH=CH Ph				MeCH=CH Ph	72	
Ph Ph				Ph Ph	60[a]	
MeCOOR	$(i\text{-Pr})_2NLi$, *n*-BuLi hexane, THF, 4 °C stir 20 min, Ar	$^{14}CO_2$(g)	Stir 30 min	$ROOCCH_2{}^{14}COOH$		1763
R = Et				R = Et	—	
R = $PhCH_2$				R = $PhCH_2$	50	
	1) $(i\text{-Pr})_2NLi$, *n*-BuLi, hexane, THF, −78 °C 2) HMPA, stir 30 min	$^{14}CO_2$(g)[b]	1) Stir 2) NH_4Cl, HCl		70[c]	1764
$F_2C{=}CH_2$	*sec*-C_4H_9Li, THF, ether, −115 °C	g	1) THF, ether (4:1), 105 °C, 10 min 2) 6*N* H_2SO_4	$F_2C{=}CHCOOH$	—	1765
$F_2C{=}CH_2$	*sec*-C_4H_9Li, THF, ether, −115 °C	g	1) THF, ether (4:1), 105 °C, 10 min. 2) RMgBr, ether 3) 6*N* H_2SO_4	$RCF{=}CHCOOH$	—	1765
			R = *n*-Et	R = Et (*E*/*Z* ratio = 87/13)	60	
			R = *n*-C_4H_9	R = *n*-C_4H_9 (*E*/*Z* ratio = 82/18)	70	
			R = Ph	R = Ph (*E*/*Z* ratio = 87/13)	51	

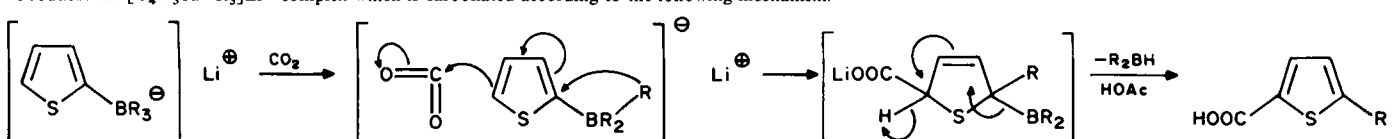
p-$RC_6H_4(CF{=}CF)_2Cl$[d]	*n*-BuLi, THF/hexane (1:1), −95 °C stir 30 min	s	1) Heat to 25 °C 2) aq. NaOH 3) aq. HCl	*p*-$RC_6H_4(CF{=}CF)_2COOH$ *trans, trans*		1766
R = Me R = MeO R = CF_3 R = Me_2N				R = Me R = MeO R = CF_3 R = Me_2N	25 23 26 51	
$RR^1C{=}C(SPh)_2$ R R^1 Me Me $-(CH_2)_5-$	$C_{10}H_8Li$, THF, −70 °C, stir 15 min	g	Stir, −70 °C	$RR^1C{=}C(SPh)COOH$ R R^1 Me Me $-(CH_2)_5-$	 49 74	1767
	*n*-BuLi, THF, hexane, N_2, −75 °C rising to −45 °C	g	Stir 5 h −95 °C rising to −65 °C			1768
E *Z*				*E* *Z*	85 71	
RCH=C=CH_2	1) *t*-BuLi, THF, −90 °C 2) $(i\text{-Bu})_3Al$[e]	g	Stir 0.5 h, −78 °C	RCH(COOH)C≡CH		1769
R = *n*-C_6H_{13} R = *c*-C_6H_{11}				R = *n*-C_6H_{13} R = *c*-C_6H_{11}	73 71	
$RCH_2C{\equiv}CH$ R = Et R = *n*-Pr R = *n*-Bu R = *n*-C_5H_{11}	*n*-BuLi, hexane, Ar, −20 °C, stir 16–24 h	s	Hexane, stir −80 °C 1.5–2 h	RC(COOH)=C=CHCOOH *cis* R = Et R = *n*-Pr R = *n*-Bu R = *n*-C_5H_{11}	 33 37 31.5 13.5	1770, 1771
n-$C_6H_{11}C{\equiv}CH$	*n*-BuLi, hexane Ar, −20 °C, stir 16–24 h	g	Stir −40 °C, 1 h	*n*-$C_6H_{11}C{\equiv}CCOOH$	26	1771
					13.5	

(*continued*)

TABLE 71 (*continued*)

Substrate	Reaction conditions for lithium reagent preparation	CO_2 g(units) or s	Reaction conditions for carbonation reaction	Product	Yield (%)	Reference
Thiophene	1) $(i\text{-Pr})_2NLi$, *n*-BuLi, THF, hexane, −78 °C, stir 1 h 2) R_3B[f]	g(25 kg/cm²)	1) Stir 2) HOAc	 R = Et, *n*-C_6H_{13}, $Me_2CH(CH_2)_{10}$	—	1772[g]
$R^2C{\equiv}CH$ R^2	1) *n*-BuLi, THF, hexane 2) R^1_3B[f] R^1	g(25 kg/cm²)	1) THF, stir, 20 °C 2) HOAc	 R^1 / R^2		1773
n-C_4H_9	*n*-C_6H_{13}			*n*-C_6H_{13} / *n*-C_4H_9	82.3	
Ph	*n*-C_6H_{13}			*n*-C_6H_{13} / Ph	71.4	
n-C_4H_9	*n*-C_8H_{17}			*n*-C_8H_{17} / *n*-C_4H_9	81.4	
Ph	*n*-C_8H_{17}			*n*-C_8H_{17} / Ph	75.6	
n-C_4H_9	*c*-C_5H_9			*c*-C_5H_9 / *n*-C_4H_9	83.7	
n-C_4H_9	*c*-C_6H_{11}			*c*-C_6H_{11} / *n*-C_4H_9	80.5	
$(EtO)_2POCH_2Cl$	1) *n*-BuLi, ether, THF, −65 °C, stir 10 min	s	Stir, 2 h	$(EtO)_2POCHClCOOH$[h]	87–91	1774

[a] Isolated as the methyl ester by treatment with diazomethane.
[b] Generated from Ba $^{14}CO_3$ upon treatment with H_2SO_4.
[c] Product was obtained in 48% radiochemical yield.
[d] As a mixture of *trans,trans: trans,cis: cis, trans* in the ratio 1:1:1.
[e] Produces the $[RCH{=}C{=}CHAl^-(Bu\text{-}i)_3]Li^+$ complex which is carbonated.
[f] Produces the $[C_4H_3SB^-R_3]Li^+$ complex which is carbonated according to the following mechanism:

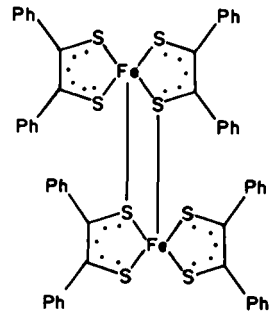


[g] Treatment of the 5-alkylthiophene-2-carboxylic acids with Raney nickel gave the corresponding alkylcarboxylic acids, $R(CH_2)_4COOH$, in good yields.
[h] Useful as a carboxychloro olefination agent for the preparation of α-chloro-α,β-ethylenic carboxylic acids from aldehydes or ketones.

carboxylic acids involves (equation 809) the treatment of dialkylaluminum halides with gaseous carbon dioxoxide at various pressures followed by acid hydrolysis. The various halides, carbon dioxide pressures and other conditions used for this reaction are reported in Table 72 along with the results obtained, which indicate that the reactivity of these reagents towards carboxylation follows the sequence: $R_3Al > R_2AlBr \sim RAlCl_2 > R'_2AlCl > R_2AlCl$ (where $R > R'$).

$$R_2AlX + CO_2(g) \longrightarrow (RCOO)RAlX \xrightarrow[HCl]{H_2O} RCOOH + RH + Al(OH)_3 + HX \quad (809)$$

Iron complexes have been used both as catalysts[1776] and as substrates[1777] in carboxylation reactions to prepare carboxylic acids. Thus, the iron–sulfur complex **186** catalyzes (equation 810) the reaction of carbon dioxide and phenylhydrazine with sulfur-containing acetates to produce[1776] α-phenylhydrazones of the corresponding carboxylic acids, which upon hydrolysis generate the corresponding α-keto acids.



(186)

$$RCH_2COS(CH_2)_7Me + CO_2(g) \xrightarrow[\substack{PhNHNH_2,\ complex\ \mathbf{186},\\ THF,\ MeOH,\ H_2O,\\ 8\ hrs}]{NaHCO_3,\ NaHS,\ THF} RCH_2C(=NNHPh)COOH \xrightarrow{hydrolysis} RCH_2COCOOH \quad (810)$$

R = H, Ph, *p*-HOC_6H_4, 3-indolyl

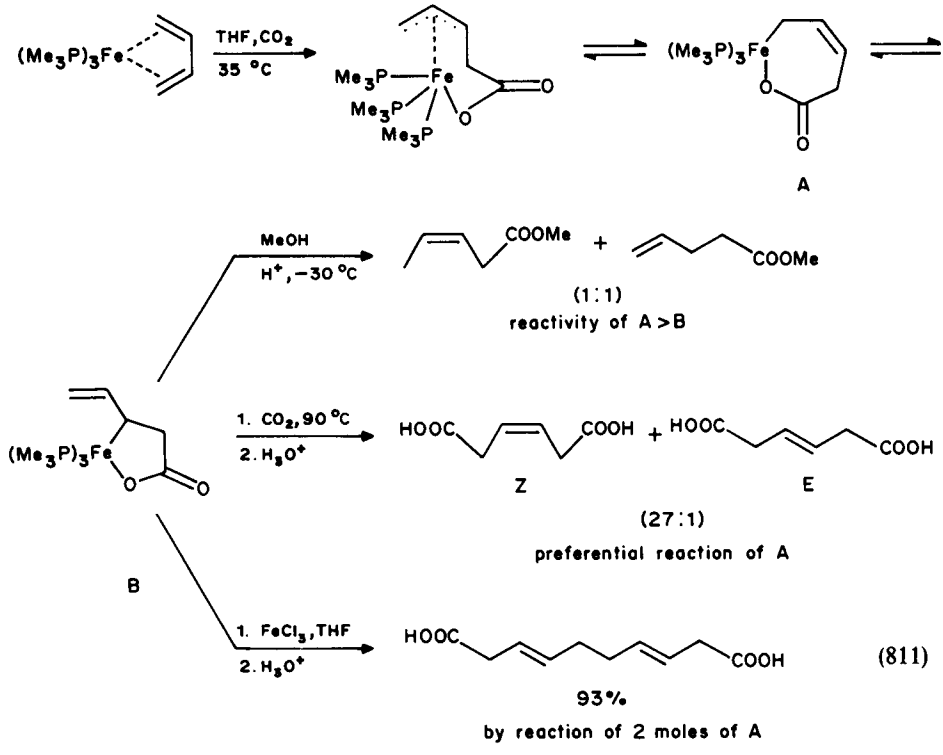
Iron(0) complexes of butadiene have been used as substrates to produce carboxylic acids or esters[1777]. Thus, reaction of (η^4-butadiene)tris(trimethylphosphane)iron(0) with gaseous carbon dioxide (3 bar) at 35 °C produces monocarboxylic acid esters or α,ω-dicarboxylic acids (equation 811) depending upon the conditions employed.

Nickel(0) complexes of 2,2′-bipyridine (1,5)-cyclooctadiene[(dipy)Ni(COD)][1778,1779] and 1,2-bis(dicyclohexylphosphino)ethane (DCPENi)[1780] have been reported to catalyze the addition of carbon dioxide to conjugated dienes to produce carboxylic acids. When the (dipy)Ni(COD) catalyst is used[1778,1779] (equation 812) monoene carboxylic acids are produced, whereas when the DCPENi catalyst is used (equation 813) diene carboxylic acids are produced. The maleic anhydride used in the second step causes the intermediate nickel carboxylates to undergo reductive elimination.

Perfluoroalkyl iodides have been converted to carboxylic acids by reaction with carbon dioxide catalyzed by zinc metal[1781] or metal couples[1782] containing zinc. Zinc metal in

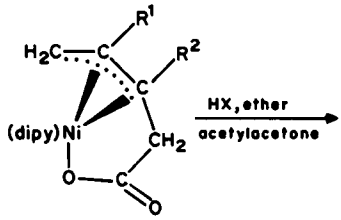
TABLE 72. Carboxylation of organoaluminum compounds[1775]

Organoaluminum substrate	Temp. (°C)	Pressure (atm)	Time (h)	Solvent	Carboxylic acid	Selectivity	Yield (%)
$(C_2H_5)_2AlCl$	140	1	4.5	*o*-Xylene	C_2H_5COOH	47	12.4
$(n\text{-}C_7H_{15})_2AlCl$	170	140	4	Dodecane	$n\text{-}C_7H_{15}COOH$	97	71
$(n\text{-}C_7H_{15})_2AlCl$	180	380	5	Decane–ether (1:2)	$n\text{-}C_7H_{15}COOH$	96	47.7
$(n\text{-}C_8H_{17})_2AlCl$	100	1	4	Decane	$n\text{-}C_8H_{17}COOH$	0	0
$(n\text{-}C_8H_{17})_2AlCl$	100	230	5	Decane–ether (1:2)	$n\text{-}C_8H_{17}COOH$	0	0
$(n\text{-}C_8H_{17})_2AlCl$	120	1	5	Decane	$n\text{-}C_8H_{17}COOH$	81	12.8
$(n\text{-}C_8H_{17})_2AlCl$	135	1	4.5	Decane	$n\text{-}C_8H_{17}COOH$	59	13.8
$(n\text{-}C_8H_{17})_2AlCl$	145	1	4.5	Decane	$n\text{-}C_8H_{17}COOH$	52.5	15.2
$(n\text{-}C_8H_{17})_2AlCl$	145	100	3	Decane	$n\text{-}C_8H_{17}COOH$	96	41.5
$(n\text{-}C_8H_{17})_2AlCl$	145	100	5	Decane	$n\text{-}C_8H_{17}COOH$	90	42
$(n\text{-}C_8H_{17})_2AlCl$	150	120	3.5	Decane–ether (1:2)	$n\text{-}C_8H_{17}COOH$	—	47
$(n\text{-}C_8H_{17})_2AlBr$	150	1	5	Dodecane	$n\text{-}C_8H_{17}COOH$	72.3	16
$(n\text{-}C_8H_{17})_2AlCl$	160	130	4	Dodecane	$n\text{-}C_8H_{17}COOH$	92	49
$(n\text{-}C_8H_{17})_2AlCl$	160–165	1	5	Decane	$n\text{-}C_8H_{17}COOH$	50	16
$(n\text{-}C_{10}H_{21})_2AlBr$	190	65	4	Dodecane	$n\text{-}C_{10}H_{21}COOH$	—	74
$(n\text{-}C_{10}H_{21})_2AlBr$	195	125	5	Dodecane	$n\text{-}C_{10}H_{21}COOH$	94.8	78.7
$(n\text{-}C_{10}H_{21})_2AlCl$	200	120	4	Dodecane:ether (1:1)	$n\text{-}C_{10}H_{21}COOH$	94	16



(811)

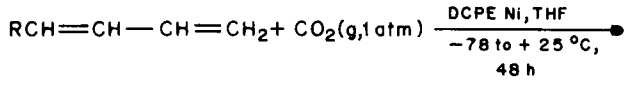
$$CH_2{=}CR^1{-}CR^2{=}CH_2 + CO_2(g) \xrightarrow[C_6H_6,\ Ar,\ -20^\circ \text{ to } 25\,^\circ C]{\text{(dipy)Ni(COD), THF, DMF or}}$$

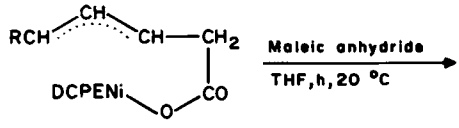


$$E\text{-}MeCR^1{=}CR^2CH_2COOH + (dipy)NiX_2 \qquad (812)$$

$R^1 =$	H	H	Me
$R^2 =$	H	Me	Me
Yield (%) =	95	—	95

combination with ultrasound has been reported[1781] to produce (equation 814) heptadecafluorooctanoic acid from heptadecarfluorooctyl iodide, while treatment of perfluoroalkyl iodides with carbon dioxide in the presence of metal couples consisting of zinc and either copper, lead, cadmium or mercury produces[1782] (equation 815) the corresponding perfluorocarboxylic acids in fair yields (Table 73).





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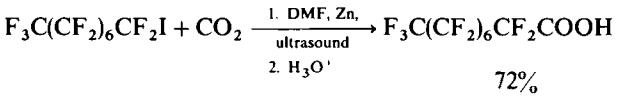

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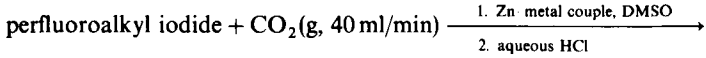
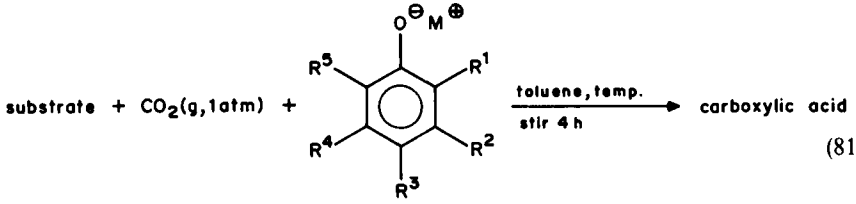


(815)

Bases alone or in combination with ammonium salts can be used to catalyze the addition of carbon dioxide to substrates possessing acidic hydrogens[1783,1784]. By using this approach ketones, esters, nitriles and nitro compounds have been converted[1783] into the corresponding carboxylic acids (equation 816) in the presence of phenoxide catalysts (Table 74), while milder bases in the presence of ammonium or phosphonium salts have been used[1784] to catalyze the addition of carbon dioxide to acetophenone, indene and fluorene to produce (equation 817) the corresponding carboxylic acids (Table 75).



(816)

TABLE 73. Preparation of perfluorocarboxylic acids by carboxylation using a zinc–copper couple catalyst[1782]

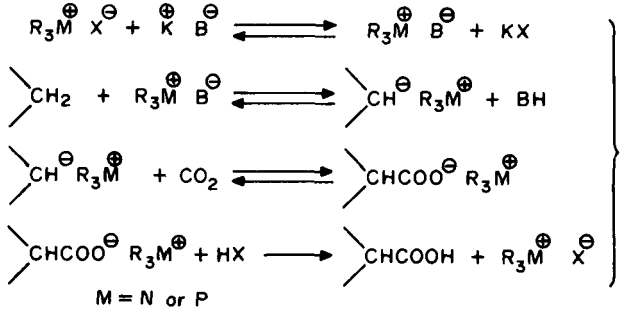
Perfluoroalkyl iodide[a]	Time (h)	Temp. (°C)	% Yield acid[b]
C_4F_9I	3	25	40
C_4F_9I	1.5	30	42
$C_6F_{13}I$	3	25	45
$C_6F_{13}I$	1.5	30	63
$C_8F_{17}I$	3	25	47

[a]Molar ratio of metal couple to iodide = 1.5:1.
[b]Based on the perfluoroalkyl iodide consumed.

TABLE 74. Phenoxide-catalyzed addition of carbon dioxide to acidic hydrogen substrates[1783]

Substrate	Phenoxide[a] M+	R1	R2	R3	R4	R5	Temp. (°C)	Product	Yield (%)
PhCOMe	K	t-Bu	H	Me	H	t-Bu	20	$PhCOCH_2COOH$	21
PhCOMe	K	t-Bu	H	Me	H	t-Bu	50	$PhCOCH_2COOH$	39
PhCOMe	K	t-Bu	H	Me	H	t-Bu	100	$PhCOCH_2COOH$	22
PhCOMe	K	t-Bu	H	Me	H	t-Bu	20	$PhCOCH_2COOH$	73[b]
PhCOMe	Na	t-Bu	H	Me	H	t-Bu	20	$PhCOCH_2COOH$	24
PhCOMe	K	t-Bu	H	t-Bu	H	t-Bu	50	$PhCOCH_2COOH$	43
PhCOMe	K	t-Bu	H	H	H	t-Bu	50	$PhCOCH_2COOH$	46
PhCOMe	K	t-Bu	H	H	H	t-Bu	20	$PhCOCH_2COOH$	12
PhCOMe	K	H	H	t-Bu	t-Bu	H	20	$PhCOCH_2COOH$	11
PhCOMe	K	t-Bu	H	H	H	H	20	$PhCOCH_2COOH$	12
PhCOMe	K	H	t-Bu	H	H	H	20	$PhCOCH_2COOH$	10
PhCOMe	K	H	H	t-Bu	H	H	20	$PhCOCH_2COOH$	6
PhCOMe	K	Ph	H	H	H	H	20	$PhCOCH_2COOH$	9
PhCOMe	K	H	H	Ph	H	H	20	$PhCOCH_2COOH$	Trace
PhCOMe	K	n-$C_{12}H_{25}$	H	H	H	H	20	$PhCOCH_2COOH$	11
PhCOMe	K	H	H	n-$C_{12}H_{25}$	H	H	20	$PhCOCH_2COOH$	Trace
PhCOMe	K	Me	H	n-$C_{12}H_{25}$	H	Me	20	$PhCOCH_2COOH$	12
PhCOMe	K	Me	H	H	H	Me	50	$PhCOCH_2COOH$	11
PhCOMe	K	H	H	H	H	H	50	$PhCOCH_2COOH$	0
MeCOMe	K	t-Bu	H	t-Bu	H	t-Bu	50	$MeCOCOOH$ + $HOOCCH_2COCH_2COOH$	15[c] 44[c]
$MeNO_2$	K	t-Bu	H	t-Bu	H	t-Bu	50	O_2NCH_2COOH	26
$PhCH_2COOMe$	K	t-Bu	H	t-Bu	H	t-Bu	50	HOOCCHPhCOOMe	36
$PhCH_2CN$	K	t-Bu	H	t-Bu	H	t-Bu	50	PhCH(CN)COOH	48
$PhCH_2CN$	K	t-Bu	H	H	H	H	20	PhCH(CN)COOH	23
$PhCH_2CN$	K	H	t-Bu	H	H	H	20	PhCH(CN)COOH	19

[a]Substrate to phenoxide molar ratio = 1:1 unless otherwise indicated.
[b]Substrate to phenoxide molar ratio = 1:3.6.
[c]Substrate to phenoxide molar ratio = 1:4.



(817)

One of the more interesting approaches to the preparation of carboxylic acids involves electrochemical carboxylation, which consists of the electrochemical reduction of selected substrates in the presence of gaseous carbon dioxide. Since in most electrocarboxylation reactions the anode is made of magnesium, this approach closely resembles the addition of carbon dioxide to Grignard reagents. The substrates used in this approach to carboxylic acid preparation range from aliphatic and aromatic halides[1785–1787] to aldehydes and ketones[1788] to α,β-unsaturated ketones[1789].

Recent reports[1785–1787] on the electrocarboxylation of halides have contained similar reaction details beginning with the fact that the anode used in all cases was made of

TABLE 75. Salt and base catalyzed addition of carbon dioxide to acidic hydrogen substrates[1784] at 25 °C

Substrate[a]	Salt	Base	Time (h)	Solvent	Yield[b](%)
Indene	$PhCH_2N^+Et_3Cl^-$	K_2CO_3	17	DMF	85
Indene	$(n\text{-}Bu)_4N^+Br^-$	K_2CO_3	17	DMF	23
Indene	$PhCH_2P^+(n\text{-}Bu)_3Cl^-$	K_2CO_3	17	DMF	17
Indene	$PhCH_2P^+(n\text{-}Bu)_3Cl^-$	K_3PO_4	17	DMF	0
Indene	$PhCH_2P^+(n\text{-}Bu)_3Cl^-$	MeCOOK	17	DMF	33
Indene	$(n\text{-}Bu)_4P^+Br^-$	K_2CO_3	17	DMF	trace
Indene	$PhCH_2N^+(n\text{-}Bu)_3Cl^-$	Na_2CO_3	17	DMF	17
Indene	$PhCH_2N^+(n\text{-}Bu)_3Cl$	Na_2CO_3	40	DMF	38
Indene	$PhCH_2N^+(n\text{-}Bu)_3Cl^-$	MeCOOK	17	DMF	25
Indene	$PhCH_2N^+(n\text{-}Bu)_3Cl^-$	$KHCO_3$	17	DMF	0
Indene	$PhCH_2N^+(n\text{-}Bu)_3Cl^-$	K_2HPO_4	20	DMF	3
Indene	$PhCH_2N^+(n\text{-}Bu)_3Cl^-$	KF	17	DMF	9
Indene	$PhCH_2N^+(n\text{-}Bu)_3Cl^-$	K_2CO_3	17	DMF + 2.4 moles H_2O	85
Indene	$PhCH_2N^+(n\text{-}Bu)_3Cl^-$	K_2CO_3	17	DMF + 9.8 moles H_2O	Trace
Indene	$PhCH_2N^+(n\text{-}Bu)_3Cl^-$	K_2CO_3	17	DMSO	84
Indene	$PhCH_2N^+(n\text{-}Bu)_3Cl^-$	K_2CO_3	40	Benzene	0
Indene	$PhCH_2N^+(n\text{-}Bu)_3Cl^-$	MeCOOK	17	Benzene	40
Indene	$PhCH_2N^+(n\text{-}Bu)_3Cl^-$	KF	17	Benzene	0
Indene	$PhCH_2N^+(n\text{-}Bu)_3Cl^-$	K_2CO_3	17	CH_2Cl_2	0
Fluorene	$PhCH_2N^+(n\text{-}Bu)_3Cl^-$	K_2CO_3	48	DMF	52
PhCOMe	$PhCH_2N^+(n\text{-}Bu)_3Cl^-$	K_2CO_3	17	DMF	42
PhCOMe	$PhCH_2N^+(n\text{-}Bu)_3Cl^-$	K_3PO_4	20	DMF	~32

[a]Carbon dioxide gas was used at 5 kg/cm^2 pressure.
[b]The acids produced were: 1,3-indenedicarboxylic acid from indene; 9-fluorenecarboxylic acid from fluorene; and benzoylacetic acid from acetophenone.

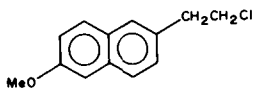
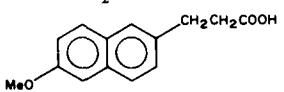
magnesium. The cathode[1787] was made from either platinum, gold, nickel, graphite or stainless steel, with stainless steel being the material of choice[1785–1787]. Aprotic solvents such as *N*-methylpyrrolidone (NMP), acetonitrile, acetone, dimethylformamide (DMF), tetrahydrofuran (THF) or a mixture of THF and hexamethylphosphoramide (HMPA) are all acceptable solvents[1785–1787], as are the following supporting electrolytes: tetra-*n*-butylammonium, fluoride, bromide, perchlorate, or tetrafluoroborate, tetraethylammonium chloride or lithium perchlorate[1785–1787]. All halide electrocarboxylation reactions were also performed using chlorides, bromides or iodides at temperatures ranging from −5 to 25 °C and involved the use of carbon dioxide at 1 atmosphere pressure[1785–1787].

The general reactions involved in this approach to carboxylic acid preparation are shown in equation 818, while the results obtained are reported in Table 76.

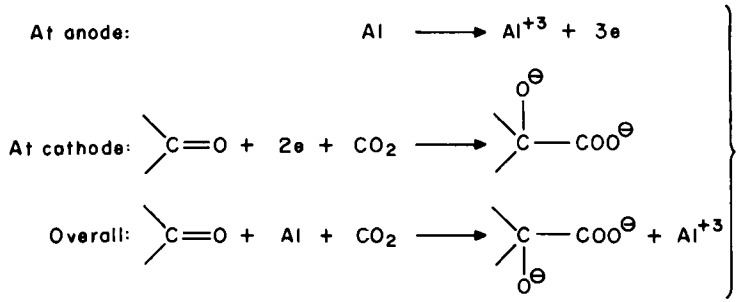
$$\left.\begin{aligned} \text{At anode:}\quad & Mg \longrightarrow Mg^{+2} + 2e \\ \text{At cathode:}\quad & RX + CO_2 + 2e \longrightarrow RCOO^{\ominus} + X^{\ominus} \\ \text{Overall:}\quad & Mg + RX + CO_2 \longrightarrow RCOO^{\ominus} + Mg^{+2} + X^{\ominus} \end{aligned}\right\} \quad (818)$$

A comparable reaction[1778] using aldehyde and ketone substrates has utilized an aluminum anode and either a zinc or graphite cathode, DMF as the solvent and tetra-*n*-butylammonium bromide as the supporting electrolyte. The general reaction involved in this case is shown in equation 819, and the results obtained are reported in Table 77.

TABLE 76. Electrocarboxylation of halides

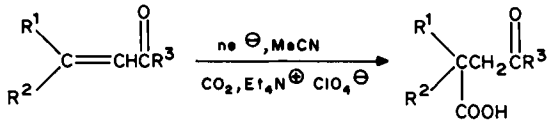
Halide	Temp. (°C)	Solvent	Acid	Yield[a] (%)	Reference
$PhCH_2Cl$	0	DMF	$PhCH_2COOH$	80–90	1786, 1787
$PhCH_2Cl$	−5	THF	$PhCH_2COOH$	90	1787
$PhCH_2Cl$	−5	Acetone	$PhCH_2COOH$	90	1787
$PhCH_2Cl$	−5	MeCN	$PhCH_2COOH$	90	1787
PhCl	−5	DMF	PhCOOH	85	1787
PhBr	−5	DMF	PhCOOH	85	1787
p-FC_6H_4Br	−5	DMF	p-FC_6H_4COOH	80	1787
p-FC_6H_4Br	40	NMP	p-FC_6H_4COOH	80	1787
2-chlorothiophene	−5	THF–HMPA	Thiophene-2-carboxylic acid	80	1787
3-Bromofuran	−5	THF–HMPA	Furan-3-carboxylic acid	78	1787
PhCHClMe	−5	DMF	PhCHMeCOOH	80	1787
n-$C_{10}H_{21}Br$	−5	DMF	n-$C_{10}H_{21}COOH$	75	1787
n-$C_{18}H_{37}Br$	−5	THF-HMPA	n-$C_{18}H_{37}COOH$	~50[b]	1787
p-BrC_6H_4COMe	−5	DMF	p-$HOOCC_6H_4COMe$	82	1787
PhCH=CHBr	−5	DMF	PhCH=CHCOOH	80	1787
$PhCH{=}CHCH_2Cl$	−5	THF–HMPA	$PhCH{=}CHCH_2COOH$	80	1787
$ClCH_2COOEt$	−5	THF	$HOOCCH_2COOEt$	~90[b]	1787
$MeCOCH_2Cl$	−5	DMF	$MeCOCH_2COOH$	~90[b]	1787
	−5	DMF		80	1787
m-$PhOC_6H_4CHClMe$	−5	DMF	m-$PhOC_6H_4CHMeCOOH$	80	1787
m-(i-C_4H_9)$C_6H_4CHClMe$	−5	DMF	m-(i-C_4H_9)$C_6H_4CHMeCOOH$	85	1787

[a]Yields of isolated acids versus the amount of consumed halide.
[b]Acid not isolated, yield was determined by acidimetry or chromotography.



(819)

Finally, there is only one report in the recent literature[1789] which utilizes the electrocarboxylation for the preparation of γ-keto acids from α,β-unsaturated ketones (equation 820, Table 78).



(820)

TABLE 77. Electrocarboxylation of aldehydes and ketones[1788]

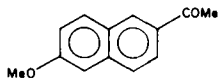
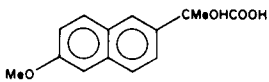
Substrate	CO (atm)	Cathode	α-Hydroxyacid	Yield (%)
PhCHO	1	Zn	PhCHOHCOOH	31–40
p-AnCHO	1	Zn	*p*-AnCHOHCOOH	32
MeCHO	5	Zn	MeCHOHCOOH	9
2-NaphCOMe	1	Graphite	2-NaphCMeOHCOOH	80
	1	Graphite		85
PhCOMe	1	Graphite	PhCMeOHCOOH	62
PhCOPh	1	Graphite	$Ph_2COHCOOH$	75

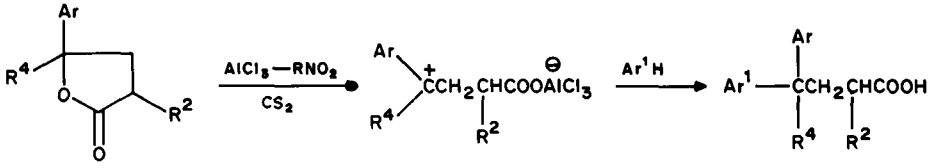
TABLE 78. Electrocarboxylation of α,β-unsaturated ketones[1789]

Ketone substrate			% Yield of products		
R^1	R^2	R^3	γ-ketoacid	Saturated ketone	dimeric products
H	Ph	Me	82	Trace	Trace
H	Ph	Ph	77	18	Trace
Ph	Ph	Ph	73	5	Trace
H	$-(CH_2)_3-$		67–18[a]	Trace	12–50[a]
Me	$-(CH_2)_3-$		10	—	80
H	H	Me	44	—	—

[a]Dependent upon the voltage used.

*F. Acids by Electrophilic Substitution Reactions

γ-Aryl-γ-lactones (**187**) can act as electrophiles, via cation **188**, in reactions with certain aromatic substrates (Ar^1H) in carbon disulfide in the presence of aluminum chloride associated with a nitro compound to give 4,4-diaryl carboxylic acids **189** (equation 821)[1790].



(821)

(187) **(188)** **(189)**

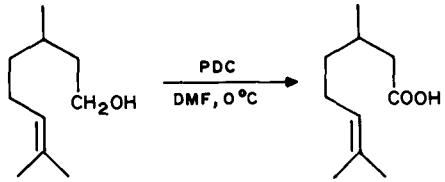
*G. Acids by Oxidation Reactions

1. Oxidation of alcohols

*a. *With base.* Several primary benzylic alcohols, including 2-naphthylmethanol, have been reported[1791] to undergo the disproportionation reaction shown in equation 822 to produce aromatic carboxylic acids, arenes and hydrogen.

$$2ArCH_2OH \xrightarrow[200\,^\circ C]{KOH(s)} ArCOOH + ArCH_3 + H_2 \qquad (822)$$

*c. *With oxides of chromium.* Pyridinium dichromate (PDC), $(C_5H_5NH^+)_2Cr_2O_7^{-2}$ precipitated as an orange solid by adding pyridine to a saturated aqueous solution of CrO_3, is a neutral, stoichiometric reagent for oxidizing nonconjugated primary alcohols to carboxylic acids in anhydrous media (equation 823)[1792]. Similar PDC oxidations of primary allylic alcohols in DMF stop at the aldehyde stage, as do oxidations of both conjugated and nonconjugated alcohols when methylene chloride is employed as solvent.



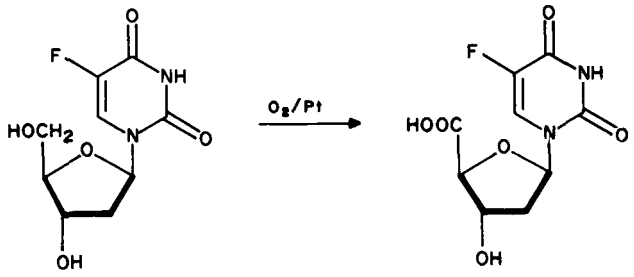
(823)

Jones' reagent in the presence of potassium fluoride in acetone can be used to convert silyl ethers of primary alcohols directly to carboxylic acids without prior cleavage of the silicon–oxygen bond (equation 824)[1793].

$$CH_3(CH_2)_{16}CH_2OSiMe_2Bu\text{-}t \xrightarrow[KF/acetone]{CrO_3/H_2SO_4} CH_3(CH_2)_{16}COOH \qquad (824)$$

*e. *With oxides of manganese.* Solid sodium permanganate monohydrate suspended in hexane effects heterogeneous oxidation of primary alcohols to carboxylic acids[1794]. Similar conditions can also be used to oxidize secondary alcohols to ketones, aldehydes to acids, sulfides to sulfones and primary amines to nitro compounds.

*h. *With air, oxygen and/or peroxides.* Oxidation of primary alcohols to carboxylic acids by means of oxygen in the presence of a platinum catalyst is illustrated by the conversion of 2'-deoxy-5-fluorouridine (**190**) to acid **191** in 92% yield (equation 825)[1795].



(190) (191) (825)

Primary and secondary alcohols as well as α,ω-glycols can be oxidized cleanly with a mixture of ozone and oxygen. Table 79 contains a representative sampling of hydroxy compounds converted to acids in this manner[1796].

Oxidation of benzylic alcohols with molecular oxygen in the presence of potassium hydroxide in 1,2-dimethoxyethane (DME) affords benzoic acids in excellent yields[1797].

Aqueous hydrogen peroxide in the presence of catalytic amounts of tungstate (WO_4^{2-}) and phosphate (PO_4^{3-}) or arsenate (AsO_4^{3-}) is highly efficient for oxidative cleavage of 1,2-diols to mono- and dicarboxylic acids (Table 80)[1798].

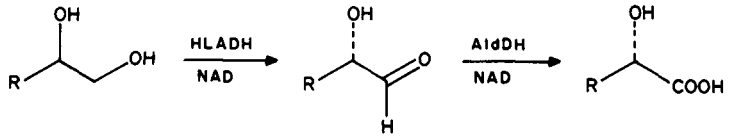
TABLE 79. Oxidation of hydroxy compounds with ozone/oxygen

Starting material	Product	Yield (%)
1-Decanol	Decanoic acid	88.6
3-Methyl-1-butanol	Isovaleric acid	82.4
1,4-Butanediol	Succinic acid	57.5
4-Nonanol	Propionic acid	15.8
	Butyric acid	33.6
	Valeric acid	14.3
	Hexanoic acid	18.5
Cyclohexanol	Adipic acid	60.2

TABLE 80. Cleavage of representative 1,2-diols to carboxylic acids with $H_2O_2/WO_4^{2-}/PO_4^{3-}$

Starting diol	Product	Yield (%)
cis-1,2-Cyclohexanediol	Adipic acid	92
trans-1,2-Cyclohexanediol	Adipic acid	94
trans-1,2-Cycloheptanediol	Pimelic acid	87
1-Phenyl-1,2-ethanediol	Bezoic acid	87
1,2-Hexanediol	Valeric acid	92

*i. *With miscellaneous reagents.* Optically pure L-α-hydroxy acids can be prepared in synthetically useful amounts from racemic 1,2-diols in an oxidation process using coimmobilized horse liver alcohol dehydrogenase (HLADH) and aldehyde dehydrogenase (AldDH) with NAD as cofactor (equation 826)[1799].



(826)

R = $HOCH_2$, FH_2C, ClH_2C, BrH_2C, Me, H_2NCH_2, $H_2C{=}CH$, Et, Me_2CH

Oxidation of primary alcohols to carboxylic acids can be effected electrochemically at a nickel hydroxide anode[1800]. Indirect electrochemical oxidation of primary alcohols to acids can be effected in an aqueous-organic two-phase system using ruthenium tetroxide/ruthenium dioxide and chlorine cation/chlorine anion redox systems. Oxidation of the alcohol by ruthenium tetroxide takes place in the organic layer and regeneration of ruthenium tetroxide from ruthenium dioxide occurs via oxidation with positive chlorine in the aqueous layer. The resulting chloride ion is then reoxidized at the anode in the aqueous phase[1801]. Aldehydes also can be oxidized to acids using this method.

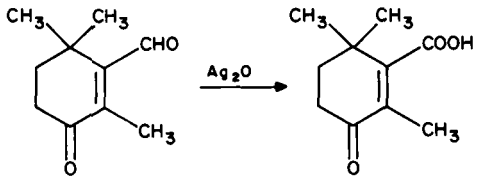
Iodosylbenzene in conjunction with ruthenium catalysts such as $RuCl_2(PPh_3)_3$ can be used as an oxidizing agent for conversion of primary alcohols and aldehydes to carboxylic acids[1802].

*2. *Oxidation of aldehydes*

*c. *With oxides of chromium.* Pyridinium dichromate[1792] oxidizes aldehydes to carboxylic acids in DMF at room temperature. Chromium(V) complexes, prepared from chromium trioxide and α,α-bipyridyl or 1,10-phenanthroline, oxidize aldehydes to acids at room temperature in methylene chloride. Oxidations of saturated and unsaturated aliphatic aldehydes proceed rapidly and without side reactions. Aromatic aldehydes also react satisfactorily, but somewhat slower than their aliphatic counterparts[1803].

*e. *With oxides of manganese.* Aromatic aldehydes containing electron withdrawing and releasing substituents undergo rapid oxidation to the corresponding carboxylic acid with benzyltriethylammonium permanganate in methylene chloride/acetic acid at room temperature. Cinnamaldehyde gives only a modest yield of cinnamic acid, and salicylaldehyde could not be oxidized[1804]. The procedure employing sodium permanganate in hexane may also be used for the oxidation of aldehydes to acids[1794].

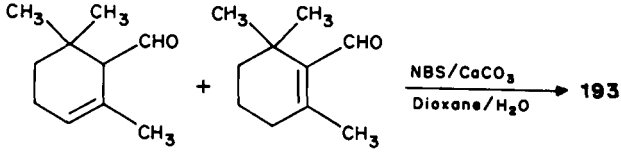
*i. *With oxides of silver.* Alkaline silver(I) oxide continues to find applications for the oxidation of aldehydes to acids. This reagent is superior to several other common



(192) (193)

(827)

oxidizing agents for the oxidation of hindered keto aldehyde **192** to keto acid **193** (equation 827)[1805]. In a related approach to **193** a mixture of α- (**194**) and β-cyclocitral (**195**) was converted to **193** in one step by oxidation with *N*-bromosuccinimide (equation 828)[1806]. Preparation of ^{13}C-labelled acid **197** involves final oxidation of aldehyde **196** with silver oxide (equation 829)[1807].



(828)

(**194**) (**195**)

$$CH_3(CH_2)_8{}^{13}CHO \xrightarrow[NaOH\ (aq)]{Ag_2O} CH_3(CH_2)_8{}^{13}COOH \qquad (829)$$

(**196**) (**197**)

**j. With miscellaneous reagents.* Several recent procedures for aldehyde to acid conversions involve the use of peroxide reagents as shown in equation 830[1808,1809]. Cerium chloride apparently catalyzes formation of the aldehyde hydrate necessary for acid formation. In the absence of cerium chloride the hydrogen peroxide–ammonium molybdate system is useful for selective oxidation of secondary alcohols in the presence of a primary alcohol[1809].

$$CH_2{=}CH(CH_2)_8CHO \xrightarrow[(NH_4)_6MoO_7\cdot 4H_2O\ /\ CeCl_3\cdot 7H_2O]{30\%\,H_2O_2} CH_2{=}CH(CH_2)_8COOH \qquad (830)$$

2-Hydroperoxyhexafluoro-2-propanol (**198**), prepared from hexafluroacetone and hydrogen peroxide, can be used stoichiometrically, or catalytically in the presence of hydrogen peroxide, for the conversion of aldehydes to carboxylic acids (equation 831)[1810]. Aromatic and aliphatic aldehydes react smoothly. Cinnamaldehyde suffers from double bond cleavage with **198**, but nonconjugated alkenals do not.

$$RCHO + CF_3\overset{\displaystyle OH}{\overset{|}{C}}CF_3 \xrightarrow[CH_2Cl_2]{Na_2CO_3} RCOOH \qquad (831)$$

(**198**)

Oxidation of α-alkylacroleins with peroxy acids proceeds smoothly to give α-alkylacrylic acids in good yields (equation 832)[1811,1812], with the rate essentially independent of the nature of R^1 and R^2.

$$CH_2{=}\overset{\displaystyle R^1}{\overset{|}{C}}CHO + R^2CO_3H \xrightarrow[10\text{–}40\,^\circ C]{\text{hydroquinone}} CH_2{=}\overset{\displaystyle R^1}{\overset{|}{C}}COOH \qquad (832)$$

R^1 = Et, Pr, *n*-Bu, *n*-Pent R^2 = Me, Et, Pr, Me_2CH

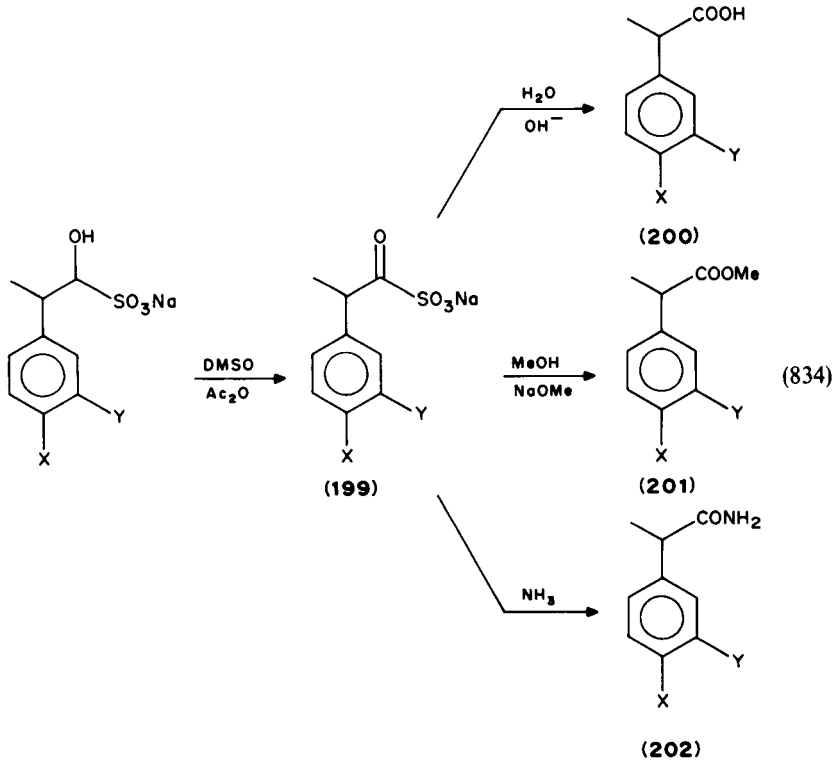
The stringent conditions (potassium hydroxide in diethylene glycol at 190 °C)

previously used for conversion of aldoximes to carboxylic acids[437,438] can be replaced by a much milder procedure in which aldoximes derived from aromatic and aliphatic aldehydes yield carboxylic acids on treatment with sodium peroxide (equation 833)[1813].

$$RCH{=}NOH + Na_2O_2 \xrightarrow[\text{steam bath}]{EtOH,\,H_2O} RCOOH \qquad (833)$$

R = Ph, *p*-anisyl, *o*-ClC_6H_4, 3-cyclohexenyl, *n*-hexyl

Aldehyde bisulfite adducts can be oxidized to acids by the action of acetic anhydride in DMSO[1814]. This oxidative pathway apparently involves initial formation of α-ketosulfonate salts **199**, which are then hydrolyzed to form acids **200**. The intermediacy of **199** is supported by the formation of esters **201** and amides **202** upon quenching the reaction mixture with sodium methoxide in methanol and ammonia, respectively (equation 834). This method is advantageous for oxidation of aldehydes in which the aldehyde function is attached to a secondary carbon, since such compounds are prone to overoxidation to form ketones with more conventional oxidizing agents[1814].



(834)

Nickel peroxide in alkaline solution is a useful oxidizing agent for the preparation of substituted benzoic acids from the corresponding benzaldehydes[1815].

Oxidation of aromatic aldehydes and α-keto acids to the corresponding carboxylic acids takes place smoothly in the presence of a flavin, thiazolium ion and cationic micelles[1816].

The low cost and minimal environmental impact of positive halogen oxidants has led to the expanded use of such reagents for the oxidation of various organic molecules,

including aldehydes. For example, in a study of the oxidation of α,β-unsaturated aldehydes, including α-methylene aldehydes, sodium chlorite in the presence of 2-methyl-2-butene as a chlorine scavenger gave the desired α,β-unsaturated acids in excellent yields (equation 835)[1817]. Aqueous hydrogen peroxide also can be employed as a chlorine trap in sodium chlorite oxidations of aldehydes[1818].

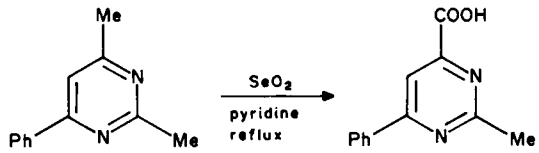
$$RCH{=}CHCHO \xrightarrow[\text{or } Na_2ClO_2, H_2O_2]{Na_2ClO_2,\ 2\text{-methyl-2-butene}} RCH{=}CHCOOH \qquad (835)$$

Saturated aliphatic and aromatic aldehydes with electron-withdrawing substituents can be oxidized with calcium hypochlorite at room temperature in aqueous acetonitrile–acetic acid[1819]. Aromatic aldehydes containing strong electron-donating groups (i.e. MeO) tend to undergo nuclear chlorination without aldehyde oxidation, while both aldehyde oxidation and chlorination of the aromatic ring take place with weak electron-donating groups (i.e., Me). α,β-Unsaturated aldehydes undergo preferential α-chlorination. Calcium hypochlorite has also been shown to be effective for the oxidation of alcohols and ethers[1820] and for the oxidative cleavage of α-diols, α-diones, α-hydroxy ketones, and α-hydroxy and α-keto acids[1821]. Aromatic aldehydes give carboxylic acids in high yields with sodium hypochloride under liquid–liquid phase transfer conditions using quaternary ammonium salts as catalysts[1822].

Potassium bromate in acetic acid effects oxidation of certain aromatic aldehydes to benzoic acids. However, ring bromination competes with oxidation when electron-donating groups are present. Salicylaldehyde, vanillin and citral did not react to give the corresponding acids, nor did aliphatic aldehydes[1823].

*3. Oxidation of arenes

*f. *With oxides of selenium.* Oxidation of polymethylpyrimidines with an equivalent of selenium dioxide in pyridine results in selective oxidation of the 4-methyl group to give pyrimidine-4-carboxylic acids (equation 836)[1824].



(836)

*g. *With other oxides of metals.* As mentioned before (Section II.G.3.g) ruthenium tetroxide is frequently used to effect degradation of the aromatic ring of arenes. It has now been discovered that when ruthenium tetroxide is used in catalytic amounts with aqueous sodium hypochlorite as the primary oxidant in a biphasic system, deactivated methylbenzenes can be oxidized to benzoic acids in good yields (equation 837)[1825]. Toluenes containing electron-donating groups give mainly ring and α-chlorinated products. Similar ruthenium oxide-catalyzed oxidations have been accomplished using sodium periodate[1826] and phenyliodosoacetate[1827] as primary oxidants in homogeneous media.

$$XC_6H_4CH_3 \xrightarrow[Bu_4\overset{+}{N}OH^-, Cl_2C_2H_4, H_2O]{NaOCl, RuO_4} XC_6H_4COOH \qquad (837)$$

X = *o*-, *m*- or *p*-NO_2; *o*- or *p*-Br; *o*- or *p*-Cl; *p*-NO; H

*h. *With air, oxygen, peroxide and/or ozone.* Aromatic carboxylic acids can be prepared from alkyl-, hydroxymethyl- and *N,N*-dimethylaminomethyl-substituted aromatics, as well as from aromatic aldehydes by oxidation with oxygen at 80–100 °C in a solution of potassium *tert*-butoxide/HMPA (equation 838)[516,1828]. In a related, but somewhat milder procedure, a similar series of substituted benzenes, naphthalenes and pyridines were oxidized by oxygen in the presence of sodium or potassium hydroxide and 18-crown-6 ether in 1,2-dimethoxyethane[1829].

$$ArX \xrightarrow{O_2,\ t\text{-BuOK/HMPA}} ArCOOH \qquad (838)$$

Ar = Ph, Naph, Pyr

X = CH_3, CH_2OH, $CH_2N(CH_3)_2$, CHO

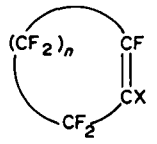
Cobalt(II) catalysts continue to be used effectively in the aerial oxidation of arylalkanes to aromatic carboxylic acids[1830–1832].

*i. *With miscellaneous reagents.* It has been observed that hydrogen peroxide in trifluoroacetic acid (TFA)[1833,1834] can be used to bring about aromatic ring oxidation of alkylbenzenes as illustrated in equation 839 by the conversion of *n*-propylbenzene to a mixture of butyric acid and acetic acid[1833,1834]. Degradation of the aromatic ring appears to result from progressive aromatic hydroxylations by positive hydroxyl groups. Pyridine and quinoline do not undergo ring degradation; instead they are converted to the respective N-oxides in good yields[1834].

$$PhCH_2CH_2CH_3 \xrightarrow[30\%\ H_2O_2]{THF} \underset{82\%}{CH_3CH_2CH_2COOH} + \underset{18\%}{CH_3COOH} \qquad (839)$$

*4. *Oxidation of double and triple bonds*

*a. *With base.* Unsaturated fluorine-containing carboxylic acids with a terminal double bond can be prepared in yields of 48–85 percent by reaction of polyfluorocycloolefins with aqueous potassium hydroxide in the presence of *tert*-butyl alcohol (equation 840)[1835].



$$\xrightarrow[H_2O,\ t\text{-BuOH},\ 25-30\ ^\circ C]{KOH} XCH{=}CF(CF_2)_nCOOH \qquad (840)$$

$n = 1–3$, X = F; $n = 3$, X = Cl

*d. *With oxides of manganese.* Several new examples of permanganate ion cleavage of carbon–carbon double bonds in biphasic systems employing phase-transfer agents have been reported[1836–1841]. The oxidative cleavage of 1-licosene to give nonadecanoic acid with potassium permanganate, sulfuric acid and acetic acid in methylene chloride using the commercially available methyltrialkylammonium chloride, Adogen 464, as the phase-transfer agent exemplifies the most convenient of these new procedures (equation 841)[1841]. Oxidative cleavage of terminal propargyl alcohols to α-hydroxy carboxylic acids with

potassium permanganate in acetic acid has been reported[1836].

$$CH_3(CH_2)_{17}CH{=}CH_2 \xrightarrow[CH_2Cl_2,H_2O]{KMnO_4,\ Adogen\ 464} CH_3(CH_2)_{17}COOH \quad (841)$$

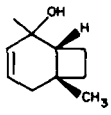
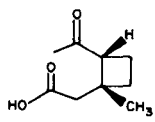
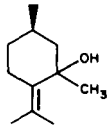
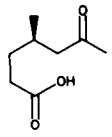
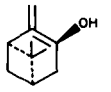
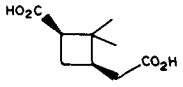
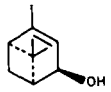
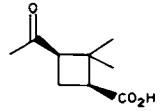
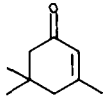
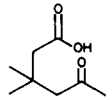
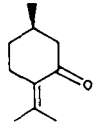
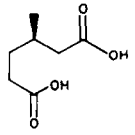
75–77%

e. With oxides of nitrogen. Reaction of α-olefins with liquid nitrogen tetroxide affords α-nitroxy acids without cleavage of the carbon–carbon double bond (equation 842)[1842].

$$RCH{=}CH_2 + N_2O_4 \xrightarrow{-10\ to\ -5\ °C} \underset{\displaystyle ONO_2}{\overset{\displaystyle |}{RCHCOOH}} \quad (842)$$

f. With oxides of ruthenium. Sharpless and coworkers[1843] reported an improved, general method for cleaving simple olefins to carboxylic acids with a catalytic amount of ruthenium oxide in the presence of acetonitrile and a stoichiometric amount of sodium periodate. More recently this method has been used for oxidative cleavage of cyclic allylic alcohols and α,β-unsaturated ketones[1844]. In these cases one or more carbons is excised from the substrate (Table 81).

TABLE 81. Oxidation of olefins, cyclic allylic alcohols and cyclic α,β-unsaturated ketones with ruthenium tetroxide[1844]

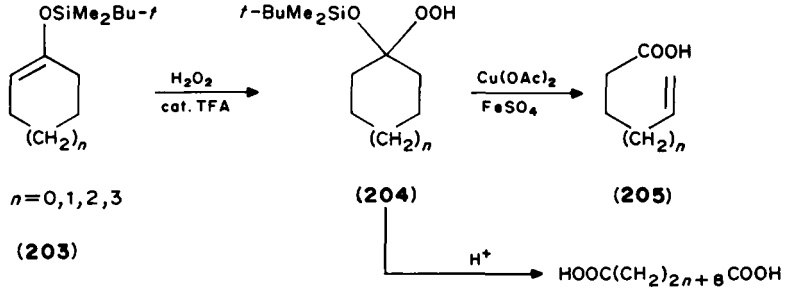
Substrate	Product	Yield (%)
		60
		66
		76
		78
		86
		92

*g. *With periodate, peroxyacids and ozone.* Two new reviews of ozonization reactions in organic chemistry were published in 1978 and 1982[1845].

A report[1846] that cycloalkenes and 1-alkenes can be converted to di- and monocarboxylic acids by ozonolysis in ethereal solvents with one molar equivalent of ozone, followed by hydrogenation over Lindlar's catalyst, appears to be in error[1847]. A more effective method for dicarboxylic acid synthesis from cycloalkenes involves ozonization of cycloalkenes in an acetic acid–formic acid mixture, followed by further oxidation with molecular oxygen[1847].

*h. *With miscellaneous reagents.* This section contains new examples of oxidation reactions of unsaturated substrates which give rise to carboxylic acids, but which do not fit into the usual categories of carbon–carbon double and triple bond cleavage.

Reaction of *t*-butyldimethylsilyl enol ethers of cyclic ketones (**203**) with hydrogen peroxide in the presence of a catalytic amount of trifluoroacetic acid gives α-silyloxy hydroperoxides **204**. Treatment of **204** with copper(II) acetate and ferrous sulfate produces unsaturated acids **205** in yields of 44–77%. When hydroperoxides **204** are reacted with ferrous sulfate, followed by aqueous acid, dicarboxylic acids **206**, arising from dimerization of intermediate ω-radicals, are produced in 54–72% yields (equation 843)[1848].



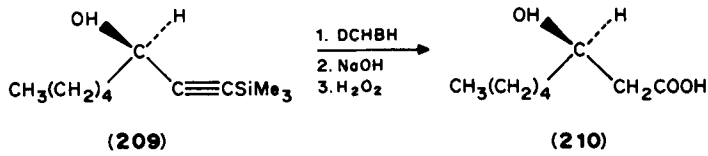
(843)

Alkenyl (alkoxy)silanes **207** derived from aldehydes undergo cleavage of the alkenyl–silicon bond with 30% hydrogen peroxide in the presence of acetic anhydride to give carboxylic acids **208** containing the same number of carbons as the original silane (equation 844)[1849]. This procedure may be viewed as a method for oxidation of aldehydes to acids. An interesting application of this oxidative procedure is shown in equation 845, where terminal acetylenes are converted to saturated carboxylic acids with the same carbon content[1849]. In effect, this sequence of reactions transforms a terminal alkyne function into a carboxymethyl group. Another method for converting the terminal carbon of an acetylene into a carboxylic acid is illustrated in equation 846 by reaction of trimethylsilylacetylene **209** with dicyclohexylborane (DCHBH), followed by oxidation, with alkaline hydrogen peroxide[1850]. The same transformation can be accomplished by the multistep reaction shown in equation 847[1851]. A procedure which allows conversion of terminal olefins to carboxylic acids with an unaltered carbon skeleton consists of hydroboration followed by chromic acid or potassium permanganate oxidation as illustrated in equation 848 by the oxidation of β-pinene to *cis*-myrtanic acid in 72% yield[1852].

$$\underset{\textbf{(207)}}{RCH{=}CHSiMe(OEt)_2} \xrightarrow[\substack{KHF_2,\,DMF\\25^\circ C}]{H_2O_2,\,Ac_2O} \underset{\textbf{(208)}}{RCH_2COOH} \qquad (844)$$

$$RC{\equiv}CH \xrightarrow[2.\ H_2PtCl_6]{1.\ HSiMe(OEt)_2} RCH{=}CHSiMe(OEt)_2$$

$$\xrightarrow[KHF_2]{H_2O_2,\,Ac_2O} RCH_2COOH \qquad (845)$$

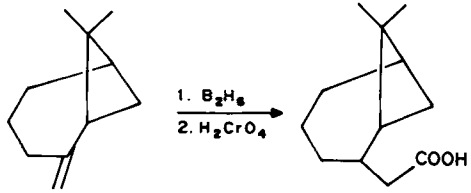


(209) (210) (846)

$$C_6H_{11}C{\equiv}CH \xrightarrow[2.\ PhSSPh]{1.\ n\text{-}BuLi} C_6H_{11}C{\equiv}CSPh$$

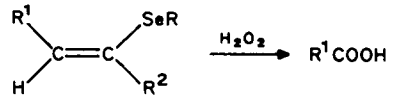
$$\xrightarrow[\substack{HOAc\\4\,h,\,80\,^\circ C}]{HgSO_4,\,H_2SO_4} C_6H_{11}CH_2COOH \qquad (847)$$

64%



(848)

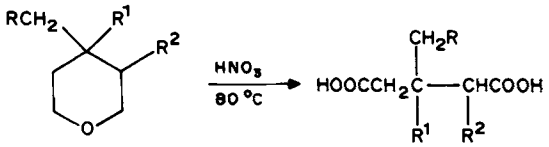
Vinyl selenides **211**, easily prepared from aldehydes and ketones, undergo oxidative cleavage with excess hydrogen peroxide to give carboxylic acids (equation 849)[1853].



(211) (849)

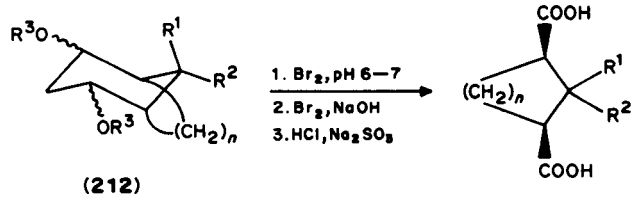
*5. *Oxidation of ethers, acetals and ketals*

g. *With miscellaneous reagents.* Oxidation of tetrahydropyrans with 50% nitric acid affords dicarboxylic acids (equation 850)[1854].



(850)

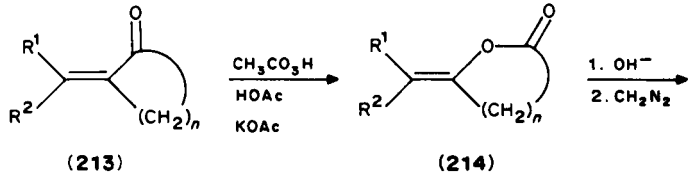
Bromine oxidation of bicyclic ethers **212** results in conversion of the 1,3-dimethoxymethylene bridge into two *cis*-carboxyl groups (equation 851)[1855]. Using this method *cis*-cyclopentane-1,3-dicarboxylic acid, *cis*-cyclohexane-1,3-dicarboxylic acid, *cis*-isoaposantenic acid and *cis*-apocamphoric acid were prepared in yields of 38–51%.



(212) (851)

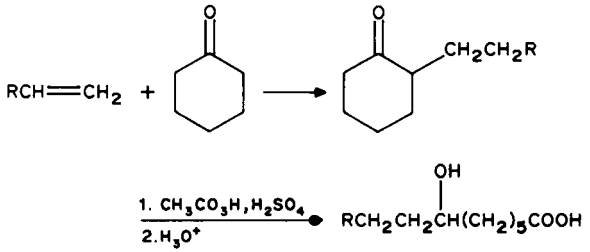
*6. *Oxidation of ketones*

a. *With peracids (Baeyer–Villiger reaction).* Baeyer–Villiger oxidation of α-alkylidenecyclanones **213** has been incorporated into a useful synthesis of keto esters and dicarboxylic esters (equation 852)[1856]. Thus, treatment of **213** with 40% peracetic acid gives enol lactones **214**. Alkaline hydrolysis of **214** followed by esterification with diazomethane leads to keto esters **215**. When this esterification step is omitted and 30% hydrogen peroxide is added to the reaction mixture, oxidative cleavage of the keto function occurs to give, after esterification with diazomethane, dicarboxylic esters **216**.



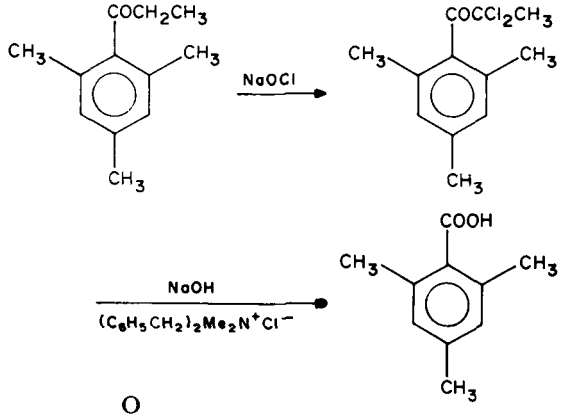
(852)

Preparation of 6-hydroxycarboxylic acids can be accomplished by initial free-radical addition of cyclohexanone to the double bond of α-olefins, followed by Baeyer–Villiger reaction of the resulting 2-alkylcyclohexanone and lactone hydrolysis (equation 853)[1857]. This method has been applied to the syntheses of 6-hydroxylauric, 6-hydroxytridecanoic, 6-hydroxymyristic, 6-hydroxypalmitic, 6-hydroxypentadecanoic, 6-hydroxystearic and 6-hydroxynonadecanoic acids.



(853)

*e. *With alkali and halogen (haloform reaction).* Haloform oxidation of acylaromatics to substituted benzoic acid can be accomplished as shown in equation 854 for 2,4,6-trimethylpropiophenone using sodium hypochlorite followed by sodium hydroxide in the presence of a phase-transfer catalyst[1858]. Haloform oxidations of methyl ketones and secondary methyl carbinols to the corresponding acids can be accomplished conveniently with sodium bromite, a stable crystalline solid (equation 855)[1859]. The versatility of this reaction is demonstrated by the variety of substrates shown in Table 82 that can be satisfactorily oxidized to acids.



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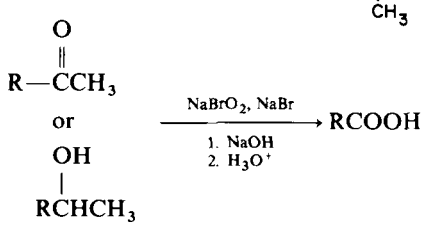


(855)

TABLE 82. Oxidation of methyl ketones and secondary alcohols to carboxylic acids with sodium bromite

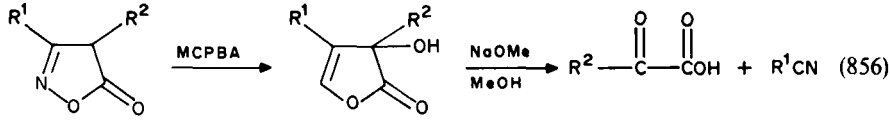
Ketone or alcohol	Product	Yield (%)
$C_2H_5COCH_3$	C_2H_5COOH	—[a]
n-$C_3H_7COCH_3$	n-C_3H_7COOH	—[a]
$(CH_3)_2CHCH_2COCH_3$	$(CH_3)_2CHCH_2COOH$	95
t-BuCOCH$_3$	t-BuCOOH	80
n-$C_5H_{11}COCH_3$	n-$C_5H_{11}COOH$	93
$C_6H_5COCH_3$	C_6H_5COOH	94
p-TolCOCH$_3$	p-TolCOOH	96
p-$ClC_6H_4COCH_3$	p-ClC_6H_4COOH	90
p-$NO_2C_6H_4COCH_3$	p-$NO_2C_6H_4COOH$	87
2-NaphCOCH$_3$	2-NaphCOOH	85
$(CH_3)_2C{=}CHCOCH_3$	$(CH_3)_2C{=}CHCOOH$	40
$C_6H_5CH{=}CHCOCH_3$	$C_6H_5CH{=}CHCOOH$	70
2-ThiCOCH$_3$	2-ThiCOOH	40
n-$C_6H_{13}CH(OH)CH_3$	n-$C_6H_{13}COOH$	40
$C_6H_5CH(OH)CH_3$	C_6H_5COOH	92

[a]Water-soluble product; yield not determined.

*7. *Oxidation of amines and lactones*

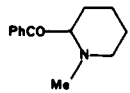
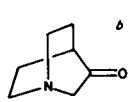
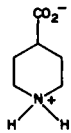
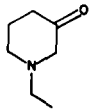
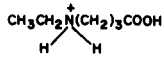
α-(*N*,*N*-Dialkyl)aminoketones undergo slow (1–14 days) but efficient oxidation with 30% hydrogen peroxide in ethanol at room temperature to give carboxylic acids in good yields as illustrated by the examples in Table 83[1859].

In an oxidative process which may be considered to be operationally analogous to a lactone oxidation, treatment of 3,4-disubstituted isoxazoline-5-ones with MCPBA followed by thermal or sodium methoxide induced fragmentation of the resulting 4-hydroxyisoxazoline-5-ones leads to formation of α-keto acids (equation 856)[1860].



(856)

TABLE 83. Oxidation of α-(*N*,*N*-dialkyl)aminoketones to carboxylic acids with hydrogen peroxide

Starting ketone	Acid product	Yield (%)
$PhCOCH_2Pip^a$	PhCOOH	94
p-$AnCOCH_2Pip^a$	p-AnCOOH	92
$PhCOC(CH_3)_2Pip^a$	PhCOOH	96
	PhCOOH	92
		72
		76

[a]Pip = piperidinyl.
[b]Oxidation was complete in 2 h.

*9. *Oxidation by microorganisms*

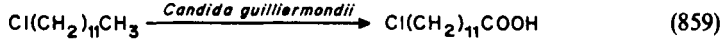
During the past decade increasing attention has been given to the synthesis of carboxylic acids by oxidative procedures utilizing either microbial agents directly or immobilized whole cell preparations containing oxidative enzymes. A review dealing with microbial oxidative metabolism of alkyl compounds for the synthesis of dibasic acids by yeasts and bacteria appeared in 1984[1861]. The use of immobilized biocatalysts for the preparation of pharmaceuticals has also been reviewed[1862]. The following examples represent a few recent applications of micrbial oxidation reactions to the synthesis of carboxylic acids.

The Japanese patent literature contains reports of the conversion of *n*-alkenes to *n*-alkene dicarboxylic acids on treatment with cultures or cells of *Candida* under aeration as

shown by the preparation of *trans*-6-dodecenedioic acid from *trans*-6-dodecene (equation 857)[1863] and the conversion of *trans*-9-octadecenoic acid to *trans*-9-octadecenedioic acid (equation 858)[1864]. Other Japanese patents describe the synthesis of ω-halocarboxylic acids by microorganism oxidation of alkyl or alkenyl halides (equation 859)[1855,1856].

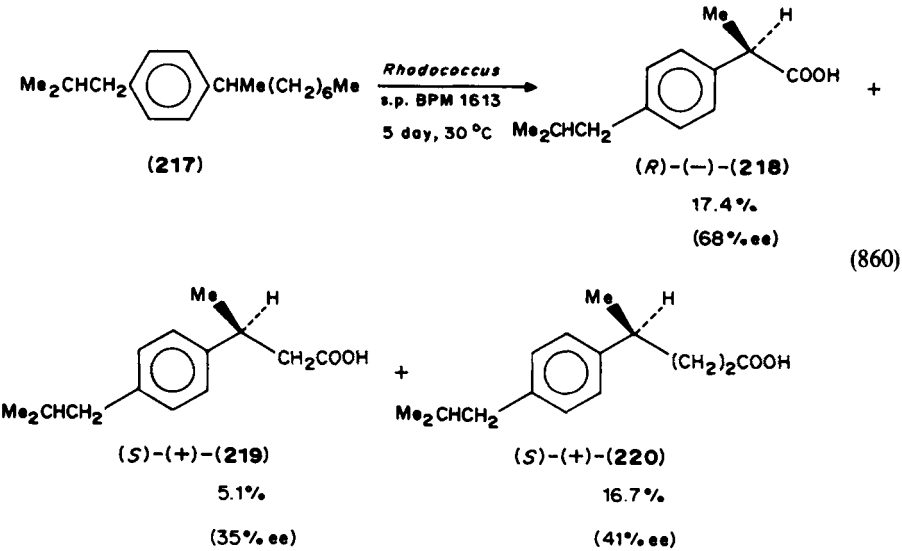
(857)

(858)



(859)

The important antiinflammatory agent (*R*)-(−)-2-(4′-isobutylphenyl)propanoic acid (ibuprofen, **218**) is obtained in 68% ee, along with acids **219** and **220**, using microbial oxidation of (+)-1-isobutyl-4-(1′-methyloctylbenzene) (**217**) by *Rhodococcus* sp. BPM 1613 (equation 860)[1867].



(860)

A study[1868] of the production of β-hydroxycarboxylic acids from aliphatic carboxylic acids by microorganisms has revealed that D(−)- and L-(+)-β-hydroxyvaleric acids can be obtained from valeric acid by *Candida rugosa* IFO 0750 and IFO 1542, respectively. β-Hydroxyisovaleric acid was produced from isovaleric acid by *Endomyces reessii* CBS 179.60. The (−) and (+) enantiomers of α-hydroxymethylbutyric acid were produced from racemic α-methylbutyric acid by *Candida rugosa* IFO 0750 and *Trichosporon fermentans*

CBS 2529, respectively; and β-hydroxyisocaproic acid was produced from isocaproic acid by *Endomyces reessii* CBS 179.60.

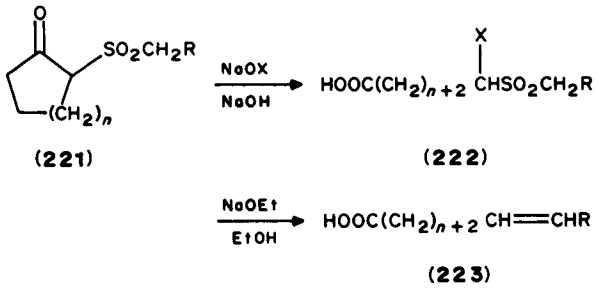
α-Keto acids can be obtained from a broad sampling of D-amino acids by oxidation with immobilized whole cells of *Trigonopsis variabilis* (equation 861)[1869,1870].

$$RCH(NH_2)COOH \xrightarrow{T.\ variabilis} RCOCOOH \qquad (861)$$

*H. Acids by Cleavage Reactions

*2. Of ketones

Unsaturated carboxylic acids **223** can be prepared by sodium hypohalite cleavage of α-(alkylsulfonyl) cycloalkanones (**221**), followed by Ramberg–Backlund rearrangement of the resulting α-halosulfones **222** (equation 862)[1871]. The position of unsaturation relative to the carboxylic group in acids **223** is determined by the ring size of the cycloalkanone.



(**221**) (**222**) (862)

(**223**)

*I. Acids by Rearrangements

*1. Arndt–Eistert and Wolff rearrangements

Benzylsulfonyldiazomethane (**224**), a stable and safe alternative to diazomethane, can be used effectively for Arndt–Eistert homologation of carboxylic acids as shown in equation 863[1872]. Reaction of **224** with acid chlorides affords α-acylated benzylsulfonyldiazomethanes **225**. Wolff rearrangement of **225** in toluene–water gives α-benzylsulfonylacetic acids **226**, which can then be desulfonylated with sodium and ethanol in tetrahydrofuran.

$$RCOCl + PhCH_2SO_2CHN_2 \longrightarrow \underset{\text{(224)}}{} RCOC(=N_2)SO_2CH_2Ph \xrightarrow[\text{toluene}]{H_2O}$$

(**225**)

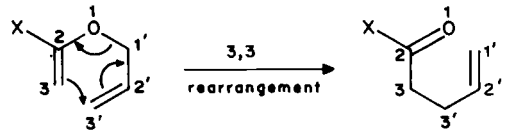
$$RCHCOOH \xrightarrow[THF]{Na,\ EtOH} RCH_2COOH \qquad (863)$$
$$SO_2CH_2Ph$$

(**226**)

*4. Claisen rearrangement

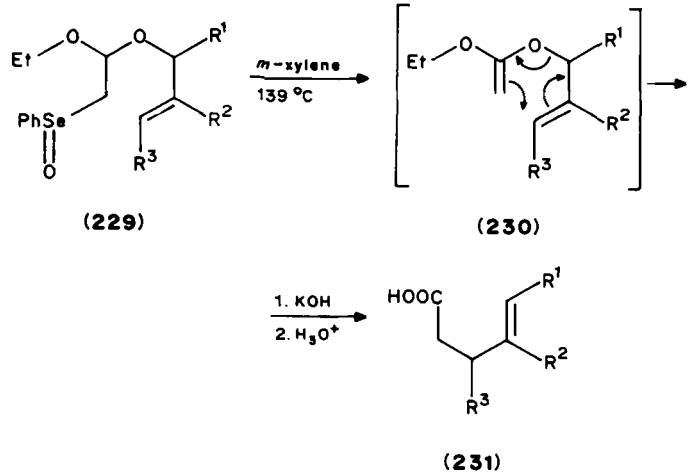
As noted in Section II.I.4, Claisen-type rearrangements[1873] had seen limited use for the synthesis of carboxylic acids and their derivatives prior to the reports of Arnold[865] and

Ireland[861] in 1972 on the ester enolate Claisen rearrangement. Since then, Claisen rearrangements have assumed a prominent role in synthesis, and have been the subject of several reviews[1874-1876]. The following examples represent some recent applications of this chemistry to the preparation of carboxylic acids. These illustrations are based on the fundamental concept that the key to successful utilization of Claisen-type[3,3]-sigmatropic rearrangements is based on access to allyl vinyl ether intermediates of type **227** (equation 864). The nature of X determines the type of carboxylic acid derivative (**228**) that will be obtained. The nature of stereochemical disposition of substituents at positions 3 and 1′–3′ in **227** determine the substitution pattern and stereochemistry of rearrangement products **228**.



(227) (228) (864)

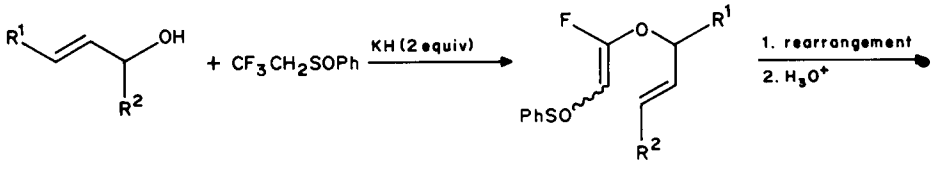
Phenylselenoxides **229** undergo elimination of benzeneselenenic acid and Claisen rearrangement in refluxing *m*-xylene in the presence of hexylamine to afford, after saponification of the crude ethyl esters, γ,δ-unsaturated acids **231** in yields of 78–100% (equation 865). Ketone acetals **230** are putative intermediates[1877].



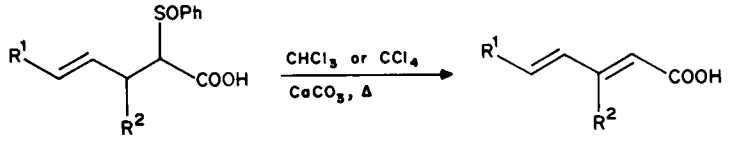
(229) (230) (231) (865)

2,4-Alkadienoic acids can be conveniently prepared by Claisen rearrangement of α-fluorovinylic ethers **232**, which are prepared *in situ* from potassium allyl alcoholates and 2,2,2-trifluoroethyphenyl sulfoxide. The fluoro group in **232** facilitates the Claisen rearrangement to the extent that simply mixing the alcoholate and the trifluoroethyl sulfoxide in THF at 0 to 5 °C and then quenching the reaction with water gives α-(phenylsulfinyl) acids **233**. Thermolysis of **233** then affords (*E,E*)-dienoic acids **234** (equation 866)[1878].

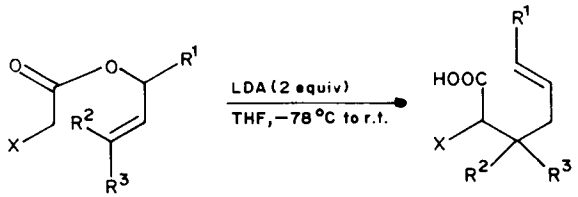
Claisen ester enolate rearrangements[861] of allyl α-hydroxyacetates (**235**, X = OH) and α-phenylthioacetates (**235**, X = SPh) give high yields of α-hydroxy (**236**, X = OH) and α-phenylthio-γ,δ-unsaturated acids (**236**, X = SPh) (equation 867)[1879].



(232) (866)



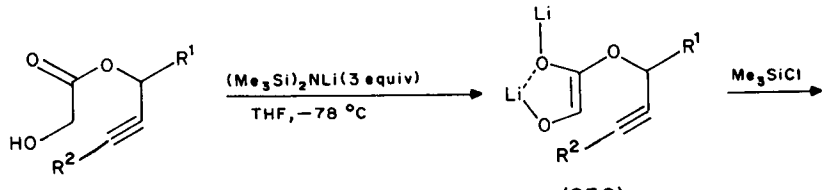
(233) (234)



(867)

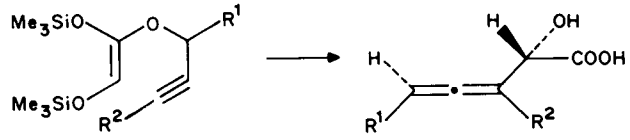
(235) (236)

Propargyl glycolates **237** undergo a related rearrangement to give 2-hydroxy-3,4-alkadienoic acids **240** via *E*-enolates **238** and bis(trimethylsiloxyl) intermediates **239** (equation 868)[1880].



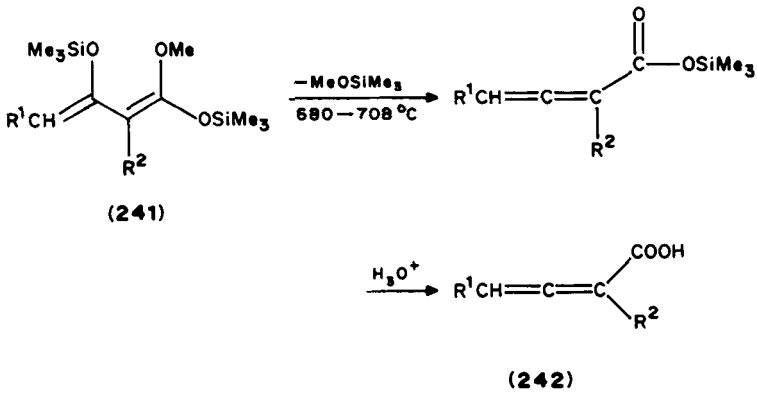
(237) (238)

(868)



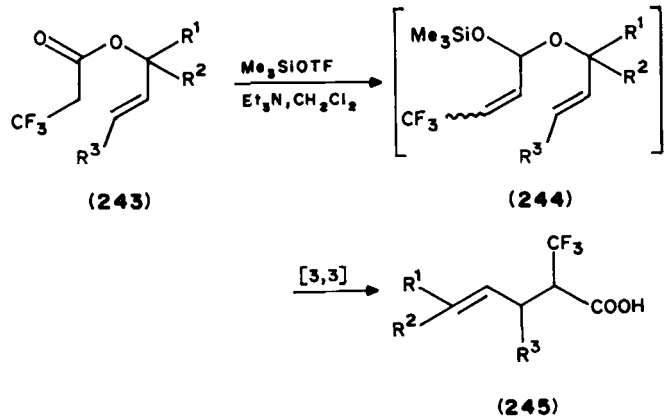
(239) (240)

2,3-Alkadienoic (α-allenic) acids **242** are available by thermal 1,5 rearrangement of 1-methoxy-1,3-bis(trimethylsiloxyl)-1,3-dienes **241**, which can be prepared from β-keto esters (equation 869)[1881].



(241) (869) (242)

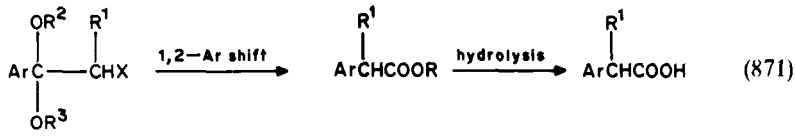
α-Allyl-α-trifluoromethylacetic acids **245** can be prepared by ester enolate Claisen rearrangement of 2-alkenyl trifluoropropionates **243** in the presence of trimethylsilyl triflate and triethylamine, which presumably convert **243** initially to trimethylsilyl enol ethers **244** (equation 870)[1882].



(243) (244) (870) (245)

*11. *Miscellaneous rearrangements*

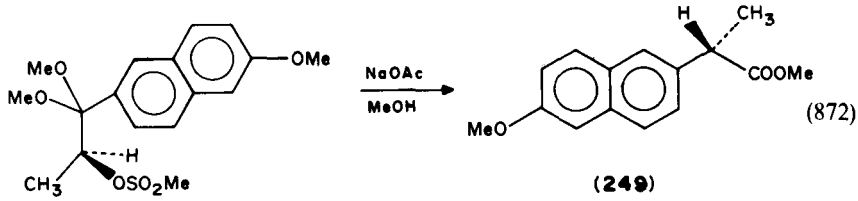
a. *Acid-catalyzed rearrangements.* The importance of 2-arylalkanoic acids **248** as antiinflammatory agents[1883–1885] has focused considerable recent attention on the synthesis of such compounds. The most widely used route to **248** involves rearrangement of α-haloalkyl aryl ketals **246** via a 1,2-aryl shift to give esters of arylalkanoic acids (**247**) which are then hydrolyzed to **248** (equation 871). Rearrangements of **246** have been effected by silver salts[1886–1888], Lewis acids[1889–1891], peracids[1892,1893], thallium nitrate[1894] and by simply heating in protic, polar solvents in the absence of acid catalysts[1895]. Similar rearrangements of aryl groups of α-tosyloxy[1896] and α-mesyloxy[1896–1898] alkyl aryl ketals can be used to produce α-arylalkanoic acids as illustrated in equation 872 by the preparation of the methyl ester of (*S*)-naproxin (**249**) with 92–97% optical purity[1897,1898].



(871)

(246) (247) (248)

X=Br or Cl



(872)

(249)

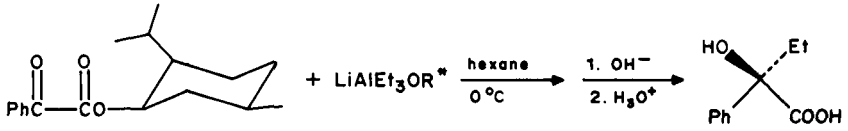
*c. *Base-catalyzed rearrangements.* Secondary (trichloromethyl) carbinols **250** have been found to undergo unimolecular rearrangement to afford α-chloracetic acids **251** on treatment with 10 percent aqueous potassium hydroxide (equation 873)[1899]. The most likely mechanism for this rearrangement appears to involve initial formation of a dichloro epoxide. Proton removal from the dichloro epoxide and ring opening to form a carbene is presumably followed by 1,2-migration of chlorine to give the carbanion of an α-chloro acid chloride, which then is protonated and hydrolyzed to give acids **251**.

$$\underset{\textbf{(250)}}{RCH(OH)CCl_3} \xrightarrow[2.\ H_3O^+]{1.\ KOH,\ 0°C} \underset{\textbf{(251)}}{RCHClCOOH} \qquad (873)$$

J. Miscellaneous Acid Synthesis

Several methods for synthesizing chiral acids were not mentioned in previous sections, as they did not correspond to the types of reactions discussed earlier. They are presented here, along with some other methodology that did not lend itself to the previous categorizations.

Reaction of chiral 'ate' complexes **253**, prepared from trimethyl- or triethylaluminum and the lithium alcoholate of (−)-*N*-methylephedrine (R*), with (−)-menthyl phenylglyoxalate (**252**) affords α-alkyl mandelic acids **254** with ee values up to 49% (equation 874)[1900].

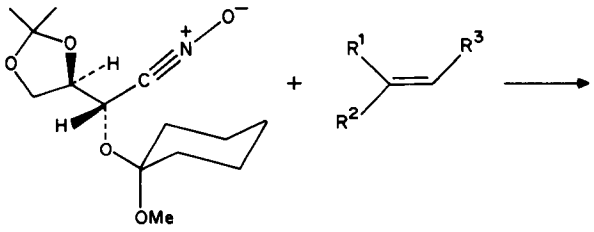


(252) (253) (*R*)-(254)

72%

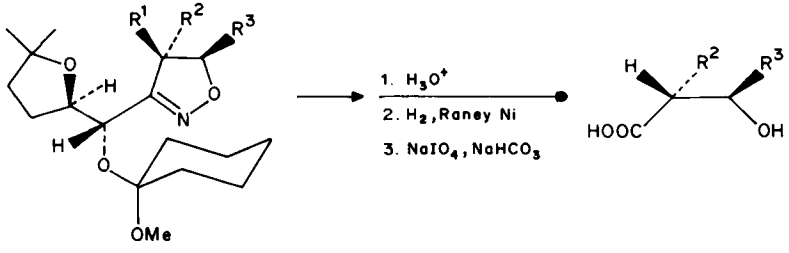
(49% ee) (874)

In an alternative to the aldol condensation approach to chiral β-hydroxy acids, chiral nitrile nitroxide **255** was reacted with a series of olefins to give diastereomeric isoxazolines **256** and **257**. Separation of diastereomers **256** and **257**, after removal of the 1-methoxycyclohexyl protecting group, followed by hydrogenolysis of the isoxazoline ring and sodium periodate cleavage of the resulting dihydroxy ketones gave optically pure acids **258** and **259** in yields of 50–77% (equation 875)[1901]. In a related cycloaddition approach to β-hydroxy acids, isoxazolines **260**, **261** and **262** were prepared by reaction of olefins with 2,2-dimethylpropanenitrile oxide, 2,2-dimethyl-2-trimethylsiloxypropanenitrile oxide and benzenesulfonylcarbonitrile oxide, respectively. Hydrogenolysis of isoxazolines **260** gave β-hydroxy *tert*-butyl ketones, which were converted to β-hydroxy *tert*-butyl esters **263** by Baeyer–Villiger oxidation (equation 876). Catalytic reduction of isoxazolinones **261** produced α'-trimethylsilyloxy β-hydroxy ketones, which were cleaved with periodic acid to β-hydroxy acids **264** (equation 877). Treatment of 3-benzenesulfonyl isoxazolines **262** with lithium methoxide afforded 3-methoxyisoxazolines, which were hydrogenolyzed to methyl esters **265** (equation 878)[1902].

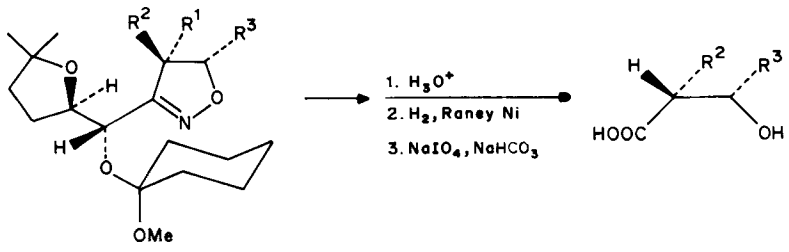


(255)

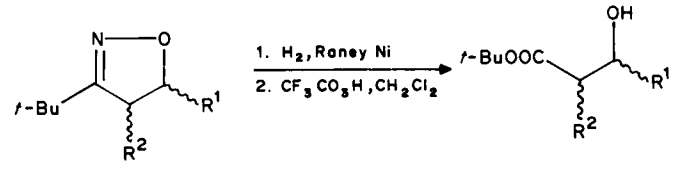
(875)



(256) (258)

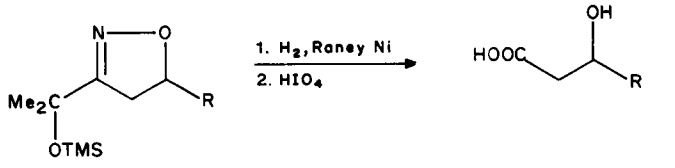


(257) (259)



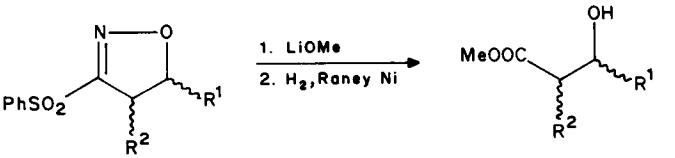
(876)

(260) (263)



(877)

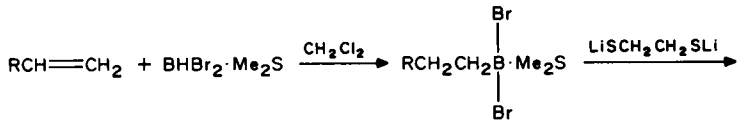
(261) (264)



(878)

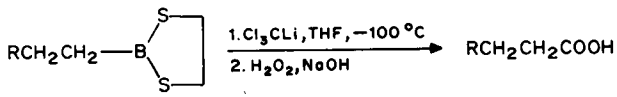
(262) (265)

Carboxylic acids can be prepared from olefins by initial hydroboration with dibromoborane–dimethyl sulfide complex, reaction of the resulting alkyldibromoborane **266** with the dilithium salt of 1,2-ethanedithiol to form 2-alkyl-1,3,2-dithiaborolanes (**267**) and then sequential treatment of **267** with trichloromethyllithium and alkaline hydrogen peroxide (equation 879)[1903].



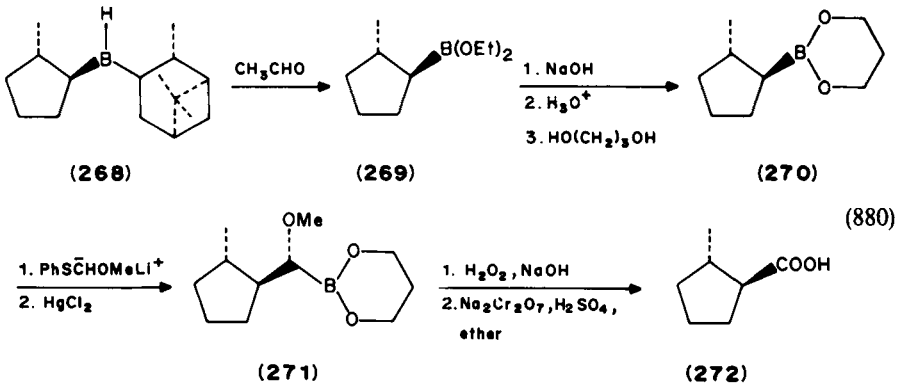
(266)

(879)



(267)

Conversion of prochiral olefins to homologous optically active acids can be accomplished by asymmetric hydroboration with monoisopinocampheylborane to give chiral isopinocamphenyl-alkylboranes such as **268** derived from 1-methylcyclopentene (equation 880). Treatment of **268** with acetaldehyde leads to boronic ester **269**. Hydrolysis of **269** followed by re-esterification with 1,3-propanediol gives optically active 2-alkyl-1,3,2-dioxaborinane **270**. Reaction of **270** with methoxy(phenylthio)methyllithium followed by mercury(II) chloride affords methoxy derivative **271**, and, in turn, the chiral acid **272** in $> 99\%$ ee[1904].

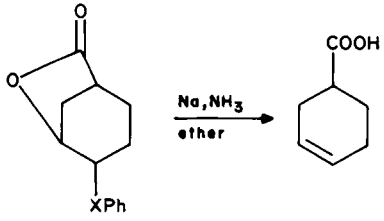


(268) (269) (270)

(271) (272)

(880)

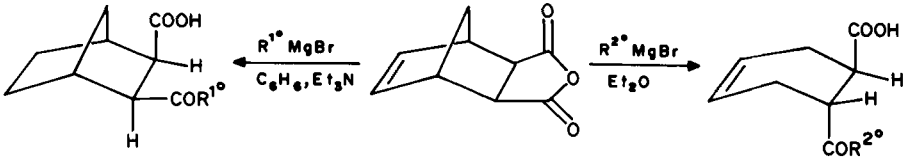
Unsaturated carboxylic acids can be obtained by a process which is in effect a reversal of phenylseleno- and phenylsulfeno-lactonization processes. For example, treatment of phenylselenyl and phenylsulfenyl lactones **273a–b** with sodium in liquid ammonia gives cyclohexenecarboxylic acid **274** in 77–79% yields (equation 881)[1905].



(273) (a) X=Se (274)
(b) X=S

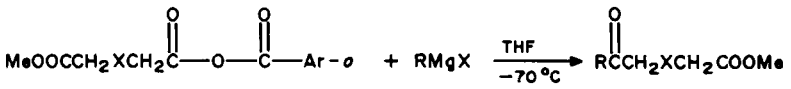
(881)

Bicyclic dicarboxylic anhydrides **275** react with secondary alkylmagnesium bromides in diethyl ether to give *trans* γ-keto acids **276**, while primary alkylmagnesium bromides in benzene/triethylamine react with **275** to give *cis* γ-keto acids **277** (equation 882)[1906]. Low temperature reactions of Grignard reagents with mixed anhydrides **278** [X = S or $(CH_2)_n$, $n = 0,1,5$] give keto esters **279** (equation 883)[1907]. However, oxa ester anhydrides **278** (X = O) failed to react.



(277) (275) (276)

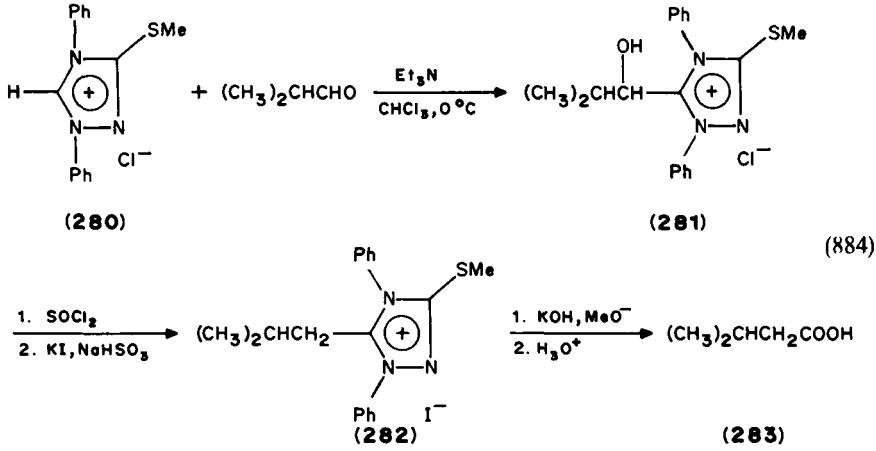
(882)



(278) (279)

(883)

Homologation of aldehydes to carboxylic acids containing one more methylene group can be effected as shown in equation 884[1908]. Thus, reaction of isobutyraldehyde with triazolium chloride **280** in the presence of triethylamine gives carbinol **281**. Treatment of **281** with thionyl chloride, followed by potassium iodide and sodium bisulfite, produces 2-alkyltriazolium iodide **282**, which is then converted to acid **283** by methanolic potassium hydroxide.



(884)

*III. SYNTHESIS OF ESTERS

The number of review articles published since 1975 which deal with the synthesis of carboxylic acid esters have been limited and are not as extensive as those dealing with the preparation of carboxylic acids. Two general review articles[1909,1910] on carboyxlic acids, esters and anhydrides have been published which consider esters as one member of a group of carboxylic acid derivatives, while one general review has been published[1911] which deals with sulfur-containing carboxylic acids, esters and anhydrides.

More specific reviews deal with the preparation and properties of vinyl carboxylates[1912], the methods of synthesis of dithiocarboxylic acids and esters[1913], carboxylic acid glucose esters[1914], the molecular design of novel activated esters, thioesters and amides for nucleophilic acyl substitution in the field of synthetic polypeptide and polymer chemistry[1915] and the carcinogenicity of esters[1916].

*A. Esters by Solvolytic Reactions

*1. *Direct esterification of acids*

A vast variety of catalysts, reagents and reaction conditions have been reported recently to effect the preparation of esters from carboxylic acids. Because of this diversity, the information contained in this section has been arranged by the similarity of the reagents or catalysts used to produce esters from carboxylic acids.

Acid-catalyzed reaction of carboxylic acids and alcohols still remains a very viable method for the preparation of esters as demonstrated by the preparation[1917] of 4-nitrazaalkanoic esters (equation 885), and methyl *p*-(4,4,4-trifluorobutyl)benzoate[1918] (equation 886), and the preparation[1919] of the alkyl esters of the polychloro poly-

fluorocarboxylic acid telomers of 1-chloro-1,2,2-trifluoroethene (equations 887 and 888).

$$\underset{\text{R}}{\underset{|}{\text{O}_2\text{NNCH}_2\text{CH}_2\text{COOH}}} + \text{EtOH} \xrightarrow[\text{r.t., 4 h}]{\text{H}_2\text{SO}_4} \underset{\text{R}}{\underset{|}{\text{O}_2\text{NNCH}_2\text{CH}_2\text{COOEt}}} \qquad (885)$$

R = Me; Et
% Yield = 45; 48

$$p\text{-F}_3\text{C(CH}_2)_3\text{C}_6\text{H}_4\text{COOH} + \text{MeOH} \xrightarrow[\substack{\text{reflux}\\ 3\text{ h}}]{\text{H}_2\text{SO}_4} p\text{-F}_3\text{C(CH}_2)_3\text{C}_6\text{H}_4\text{COOMe} \qquad (886)$$

92%

$$\text{X(CFClCF}_2)_n\text{COOH} + \text{ROH} \xrightarrow{\text{H}_2\text{SO}_4} \text{X(CFClCF}_2)_n\text{COOR} \qquad (887)$$

X = Cl; Cl; Br
n = 1; 3; 1
R = Et; Me; Et

$$\text{Cl}_3\text{CCF}_2\text{COOH} + \text{EtOH} \xrightarrow{\text{H}_2\text{SO}_4} \text{Cl}_3\text{CCF}_2\text{COOEt} \qquad (888)$$

The use of dicyclohexyl carbodiimide (DCCD) has been reported for a wide variety of acid substrates (equation 889) as reported in Table 84.

$$\text{RCOOH} + \text{R'OH} \xrightarrow{\text{DCCD}} \text{RCOOR'} \qquad (889)$$

Sulfur-containing reagents ranging from sulfuryl chloride fluoride to δ-quinolinesulfonyl tetrazolide have been used as coupling reagents to catalyze the condensation of carboxylic acids and alcohols. Thus benzaldehyde-sulfuric acid has been used[1925] in the condensation of oleic acid with methanol (equation 890), while p-toluenesulfonic acid has been used[1926,1927] in the condensation of stearic acid with methanol. In the latter case, pretreatment of the stearic acid with either 85% phosphoric acid[1926] (equation 891) or 30% hydrogen peroxide[1927] (equation 892) is recommended for improving the yield of the methyl stearate.

$$\text{Me(CH}_2)_7\text{CH=CH(CH}_2)_7\text{COOH} + \text{MeOH} \xrightarrow[\substack{o\text{-HOCC}_6\text{H}_4\text{SO}_3\text{H}\\ 6\text{ h}}]{\text{PhOH, 70°C}} \qquad (890)$$

$$\text{Me(CH}_2)_7\text{CH=CH(CH}_2)_7\text{COOMe}$$

85.3%

$$\text{Me(CH}_2)_{16}\text{COOH} \xrightarrow[\text{2. MeOH, } p\text{-MeC}_6\text{H}_4\text{SO}_3\text{H, 50°C, reflux 10 h}]{\text{1. 85\% H}_3\text{PO}_4\text{, stir 120°C, 30 min}} \text{Me(CH}_2)_{16}\text{COOMe} \qquad (891)$$

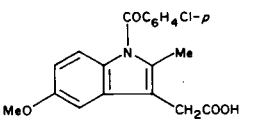
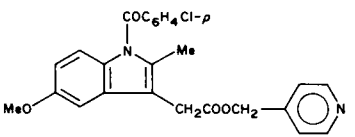
98.4%

$$\text{Me(CH}_2)_{16}\text{COOH} \xrightarrow[\text{2. MeOH, } p\text{-MeC}_6\text{H}_4\text{SO}_3\text{H, 10 h}]{\text{1. 30\% H}_2\text{O}_2\text{, 100°C, 30 min}} \text{Me(CH}_2)_{16}\text{COOMe} \qquad (892)$$

98.5%

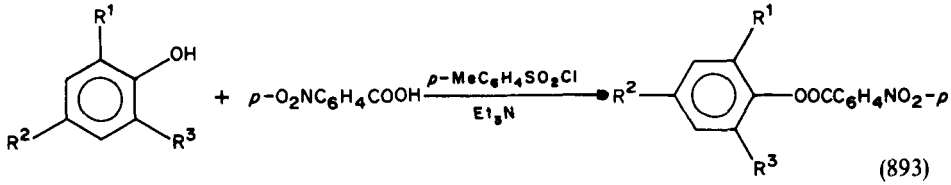
(94.9% without prior H_2O_2 pretreatment)

TABLE 84. Preparation of esters using dicyclohexeylcarbodiimide

Acid	Alcohol	Reaction conditions[a]	Product	Yield (%)	Reference
MeCOOH	*t*-BuOH	NPP, ether or CH_2Cl_2, r.t., 3 h	MeCOOBu-*t*	90	1921
MeCOOH	*p*-$O_2NC_6H_4OH$	—	$MeCOOC_6H_4NO_2$-*p*	—	1920
$Me(CH_2)_8COOH$	*p*-$O_2NC_6H_4OH$	—	$Me(CH_2)_8COOC_6H_4NO_2$-*p*	—	1920
$Me(CH_2)_{10}COOH$	*p*-$O_2NC_6H_4OH$	—	$Me(CH_2)_{10}COOC_6H_4NO_2$-*p*	—	1920
$Me_2CHCOOH$	*t*-BuOH	NPP, ether or CH_2Cl_2, r.t., 24 h	$Me_2CHCOOBu$-*t*	65	1921
Me_3CCOOH	*p*-$O_2NC_6H_4OH$	—	$Me_3CCOOC_6H_4NO_2$-*p*	—	1920
c-$C_6H_{11}COOH$	*p*-$O_2NC_6H_4OH$	—	*c*-$C_6H_{11}COOC_6H_4NO_2$-*p*	—	1920
$Ph(CH_2)_2COOH$	*p*-$O_2NC_6H_4OH$	—	$Ph(CH_2)_2COOC_6H_4NO_2$-*p*	—	1920
$Ph(CH_2)_4COOH$	*p*-$O_2NC_6H_4OH$	—	$Ph(CH_2)_4COOC_6H_4NO_2$-*p*	—	1920
$Ph_2CHCOOH$	EtOH	NPP, ether or CH_2Cl_2, r.t., 12 h	$Ph_2CHCOOEt$	96	1921
PhCOOH	EtOH	NPP, ether or CH_2Cl_2, r.t., 0.5 h	PhCOOEt	90	1921
PhCOOH	PhOH	NPP, ether or CH_2Cl_2, r.t., 6 h	PhCOOPh	94	1921
p-$BrC_6H_4CH_2COOH$	EtOH	NPP, ether or CH_2Cl_2, r.t., 12 h	*p*-$BrC_6H_4CH_2COOEt$	96	1921
2,4,6-$Me_3C_6H_2COOH$	*p*-$O_2NC_6H_4OH$	NPP, ether or CH_2Cl_2, r.t., 12 h	2,4,6-$Me_3C_6H_2COOC_6H_4NO_2$-*p*	90	1921
PhCONHCH(Me)COOH	$PhCH_2OH$	NPP, ether or CH_2Cl_2, r.t., 2 h	$PhCONHCH(Me)COOCH_2Ph$	80	1921
$PhCH_2OCONHCH(Me)COOH$	*o*-$O_2NC_6H_4CH_2OH$	NPP, ether or CH_2Cl_2, r.t., 2 h	$PhCH_2OCONHCH(Me)COOCH_2C_6H_4NO_2$-*o*	78	1921
$PhCH_2OCONHCH(CH_2Ph)COOH$	*o*-$O_2NC_6H_4OH$	NPP, ether or CH_2Cl_2, r.t., 1 h	$PhCH_2OCONHCH(CH_2Ph)COOC_6H_4NO_2$-*o*	71	1921
EtOOCCH=CHCOOH (*trans*)	*t*-BuOH	DMAP, CH_2Cl_2, r.t., 3 h	EtOOCCH=CHCOOBu-*t*	76–81	1922
	4-$PyrCH_2OH$	CH_2Cl_2, stir overnight		51	1923
p-$(ClCH_2CH_2)_2NC_6H_4CH_2COOH$	3-Hydroxyandrost-5-en-17-one (3-HOAND)	DMAP or pyridine, CH_2Cl_2	*p*-$(ClCH_2CH_2)_2NC_6H_4CH_2COO$ (3-OAND)	—	1924
p-$(ClCH_2CH_2)_2NC_6H_4OCH_2COOH$	3-HOAND	DMAP or pyridine CH_2Cl_2	*p*-$(ClCH_2CH_2)_2NC_6H_4OCH_2COO$ (3-OAND)	—	1924

[a]NPP = *N*-(4-pyrridyl)pyrrolidine; DMAP = 4-dimethylamino pyridine; Pyr = pyridyl.

p-Toluenesulfonyl chloride has been reported[1928] to catalyze the esterification of phenols (equation 893) and naphthols (equations 894 and 895) with *p*-nitrobenzoic acid in the presence of triethylamine. However, when a similar condensation of 2,4-dinitrophenol and *p*-nitrobenzoic acid was attempted[1928] it was found that *p*-toluenesulfonyl chloride in the presence of Dabco (triethylenediamine) was required (equation 896) to effect reaction.

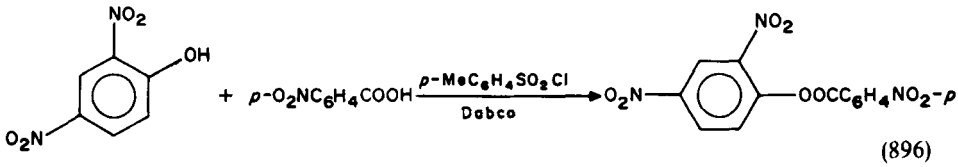


(893)

$R^1=R^2=R^3=H,Me,Cl$
$R^1=Cl,R^2=R^3=H$

$$1\text{-NaphOH} + p\text{-}O_2NC_6H_4COOH \xrightarrow[Et_3N]{p\text{-}MeC_6H_4SO_2Cl} 1\text{-NaphOOCC}_6H_4NO_2\text{-}p \quad (894)$$

$$2\text{-NaphOH} + p\text{-}O_2NC_6H_4COOH \xrightarrow[Et_3N]{p\text{-}MeC_6H_4SO_2Cl} 2\text{-NaphOOCC}_6H_4NO_2\text{-}p \quad (895)$$



(896)

A variety of esters have been prepared[1929] by the sulfuryl chloride fluoride mediated esterification of carboxylic acids with alcohols. This method proceeds through the formation of the corresponding acyl fluorosulfonate which is generated *in situ* and then allowed to react with the alcohol (equation 897).

$$R^1COOH + SO_2ClF \xrightarrow[N_2,\ r.t,\ stir\ 1\ h]{CH_2Cl_2,\ Et_3N} [R^1COOSO_2F] \xrightarrow[stir\ 2\ h]{R^2OH,\ Et_3N} R^1COOR^2 \quad (897)$$

R^1	R^2	Product	Yield (%)
Ph	$PhCH_2$	$PhCOOCH_2Ph$	80
Ph	Ph	PhCOOPh	75
Ph	Me	PhCOOMe	67
p-ClC_6H_4	Me	*p*-ClC_6H_4COOMe	89
Ph	Et	PhCOOEt	55
p-ClC_6H_4	Et	*p*-ClC_6H_4COOEt	91
PhCH=CH	$PhCH_2$	$PhCH=CHCOOCH_2Ph$	84
p-$O_2NC_6H_4CH=CH$	Me	*p*-$O_2NC_6H_4CH=CHCOOMe$	82
$MeOCH_2$	Et	$MeOCH_2COOEt$	51

2-Fluoro-2,2-dinitroethyl hydrogen sulfate[1930] (equation 898) and [(1,1,7-trihydrododecafluoroheptyl)oxy] trifluorosulfurane[1931] (equation 899) have both been reported to react directly with carboxylic acids to produce the corresponding esters.

$$R^1COOR^2 + (O_2N)_2CFCH_2OSO_3H \rightarrow R^1COOCH_2CF(NO_2)_2 \quad (898)$$

$R^1 = H, Me, CH_2{=}CH, CH_2{=}CMe, n\text{-}C_{11}H_{23}$

$R^2 = H, Na^+, K^+, alkyl$

$$RCOOH + F_3C(CF_2)_5CH_2O\overset{\oplus}{S}F_2X^{\ominus} \xrightarrow[0\text{–}20\,^\circ C]{\text{Freon 113}} RCOOCH_2(CF_2)_5CF_3 \quad (899)$$

$R = Me, Ph; \quad X^{\ominus} = HF_2^{\ominus}, BF_4^{\ominus}, SbF_6^{\ominus}$

Reaction of benzyl alcohol and benzoic acid in the presence of 8-quinolinesulfonyl tetrazolide (8-QST) as a coupling agent afforded[1932] benzyl benzoate in 89% yield (equation 900).

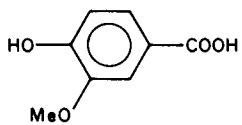
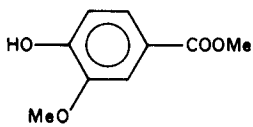
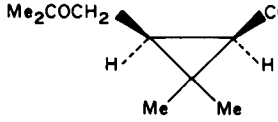
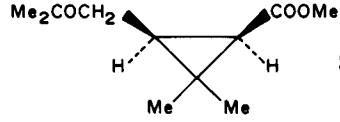
$$PhCOOH + PhCH_2OH + \text{8-QST} \xrightarrow[\text{2. warm to r.t., stir 1 h}]{\text{1. } NEt_3,\ CH_2Cl_2,\ 0\ ^\circ C} PhCO_2CH_2Ph \quad (900)$$

89%

Dimethyl sulfate has also been used[1933] to produce methyl esters from a variety of carboxylic acids (equation 901).

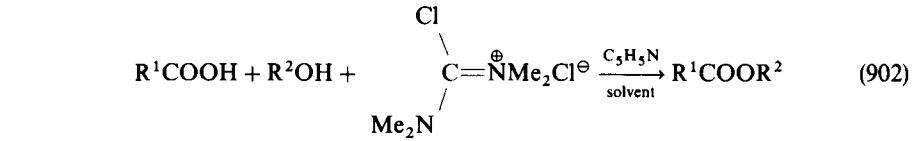
$$RCOOH + Me_2SO_4 \xrightarrow[\text{method}]{Me_2CO,\ NaHCO_3} RCOOMe \quad (901)$$

Method: A = reflux;
B = continuous stirring at room temperature.

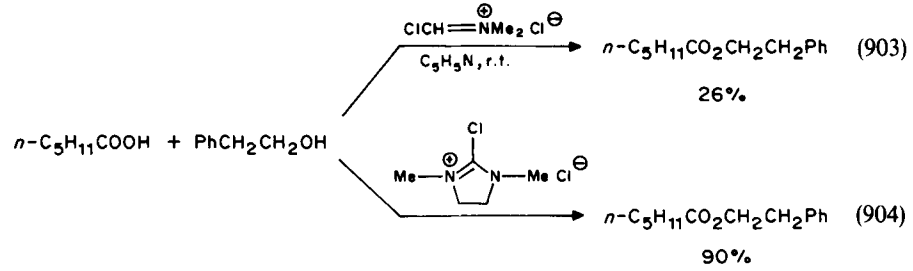
Acid	Rx time (h)	Method	Product	Yield (%)
p-HOC_6H_4COOH	20	A	*p*-HOC_6H_4COOMe	92
	24	A		89
$3,5\text{-}(HO)_2C_6H_3COOH$	10	A	$3,5\text{-}(HO)_2C_6H_3COOMe$	93
$3,4\text{-}(HO)_2C_6H_3COOH$	15	A	$3,4\text{-}(HO)_2C_6H_3COOMe$	95
$3,4,5\text{-}(MeO)_3C_6H_2COOH$	6	A	$3,4,5\text{-}(MeO)_3C_6H_2COOMe$	97
$PhCH_2COOH$	7	A	$PhCH_2COOMe$	96
$PhOCH_2COOH$	12	A	$PhOCH_2COOMe$	96
$Me(CH_2)_{16}COOH$	48	A	$Me(CH_2)_{16}COOMe$	95
	30	B		85

Nitrogen-containing compounds are efficient condensation reagents for esterification. For example, *N,N,N',N'*-tetramethylchloroformamidinium chloride, easily prepared from *N,N,N',N'*-tetramethylurea and oxalyl chloride, has been used[1934] in a one-pot esterific-

ation of carboxylic acids (equation 902 and Table 85). Some examples (equations 903 and 904) of esterification reactions using similar reagents are also reported in the same article[1934].



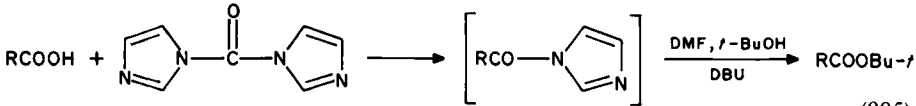
(902)



(903)

(904)

The preparation of *t*-butyl carboxylates has always been complicated by the inconvenience in handling the reagents required and/or the limited range of applicability of the available methods. Because of this, the otherwise useful method of treating *N*-acylimidazole (formed by reaction of carboxylic acids with *N,N'*-carbonyldiimidazole) with *t*-butyl alcohol in the presence of sodium *t*-butoxide[1935] would find extensive use were it is not for the fact that this approach is not applicable to alkanoic acids possessing one or two hydrogen atoms at C-2 because of the competitive formation of 3-oxoalkanoic



(905)

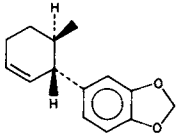
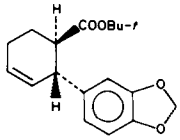
R	Temp (°C)	Time (h)	Product	Yield (%)
Ph	40	5	PhCOOBu-*t*	91
o-ClC_6H_4	40	24	*o*-ClC_6H_4COOBu-*t*	85
$Ph(CH_2)_3$	40	10	$Ph(CH_2)_3COOBu$-*t*	75
3-Pyr	40	6	3-PyrCOOBu-*t*	84
n-C_6H_{13}	40	5	*n*-$C_6H_{13}COOBu$-*t*	76
$Me(CH_2)_2CH(Me)$	40	24	$Me(CH_2)_2CH(Me)COOBu$-*t*	85
c-C_6H_{11}	40	15	*c*-$C_6H_{11}COOBu$-*t*	74
PhCH=CH	40	24	PhCH=CHCOOBu-*t*	64
2-FuCH=CH	40	24	2-FuCH=CHCOOBu-*t*	54
	80	5		68

TABLE 85. Esterifications using *N,N,N',N'*-tetramethylchloroformamidinium chloride[1934]

Acid	Alcohol	Solvent	Rx time	Product	Yield (%)
n-$C_5H_{11}COOH$	$PhCH_2CH_2OH$	$ClCH_2CH_2Cl$	45 min	n-$C_5H_{11}COOCH_2CH_2Ph$	97
i-PrCOOH	$PhCH_2CH_2OH$	$ClCH_2CH_2Cl$	18 h	i-$PrCOOCH_2CH_2Ph$	93
t-BuCOOH	$PhCH_2CH_2OH$	$ClCH_2CH_2Cl$	18 h	t-$BuCOOCH_2CH_2Ph$	90
n-$C_5H_{11}COOH$	$PhCH_2CH(Me)OH$	$ClCH_2CH_2Cl$	2 h	n-$C_5H_{11}COOCH(Me)CH_2Ph$	85
n-$C_5H_{11}COOH$	s-BuOH	$ClCH_2CH_2Cl$	2 h	n-$C_5H_{11}COOBu$-s	79
n-$C_5H_{11}COOH$	t-BuOH	$ClCH_2CH_2Cl$	16 h	n-$C_5H_{11}COOBu$-t	77
n-$C_5H_{11}COOH$	$Me_2C{=}CHCH_2OH$	$ClCH_2CH_2Cl$	4 h	n-$C_5H_{11}COOCH_2CH{=}CMe_2$	87
MeCH=CHCOOH (*trans*)	$PhCH_2CH_2OH$	MeCN	18 h	MeCH=CHCOOCH_2CH_2Ph (*trans*)	66
PhCOOH	$PhCH_2CH_2OH$	MeCN	20 h	$PhCOOCH_2CH_2Ph$	91

esters. However, a recent report[1936] reveals that reaction of the intermediate *N*-acylimidazole, generated *in situ*, with *t*-butyl alcohol can be effected by using 1,8-diazabicyclo [5.4.0]-7-undecene (DBU) as the base instead of sodium *t*-butoxide (equation 905).

Diethyl azodicarboxylate (DEAD) and 3-methylbenzothiazole-2-selone (MBT Se) together have been used[1937] to catalyze intermolecular dehydration between carboxylic acids and alcohols to produce (equation 906) the corresponding esters with retention of configuration of the alcohol (Table 86). A similar catalyst[1938] is 2-halo-3-ethylbenzothiazolium fluoroborate, which produces an intermediate, 1-ethyl-2-benzothiazoliumcarboxylate, which then reacts with the added alcohol in the presence of an amine base to produce the ester (equation 907 and Table 87). An interesting alternative approach[1938] involves the reaction of the 2-halo-3-ethylbenzothiazolium fluoroborate with the alcohol first producing 1-ethyl-2-benzothiazolium ester salt, which then reacts with the carboxylic acid (equation 908).

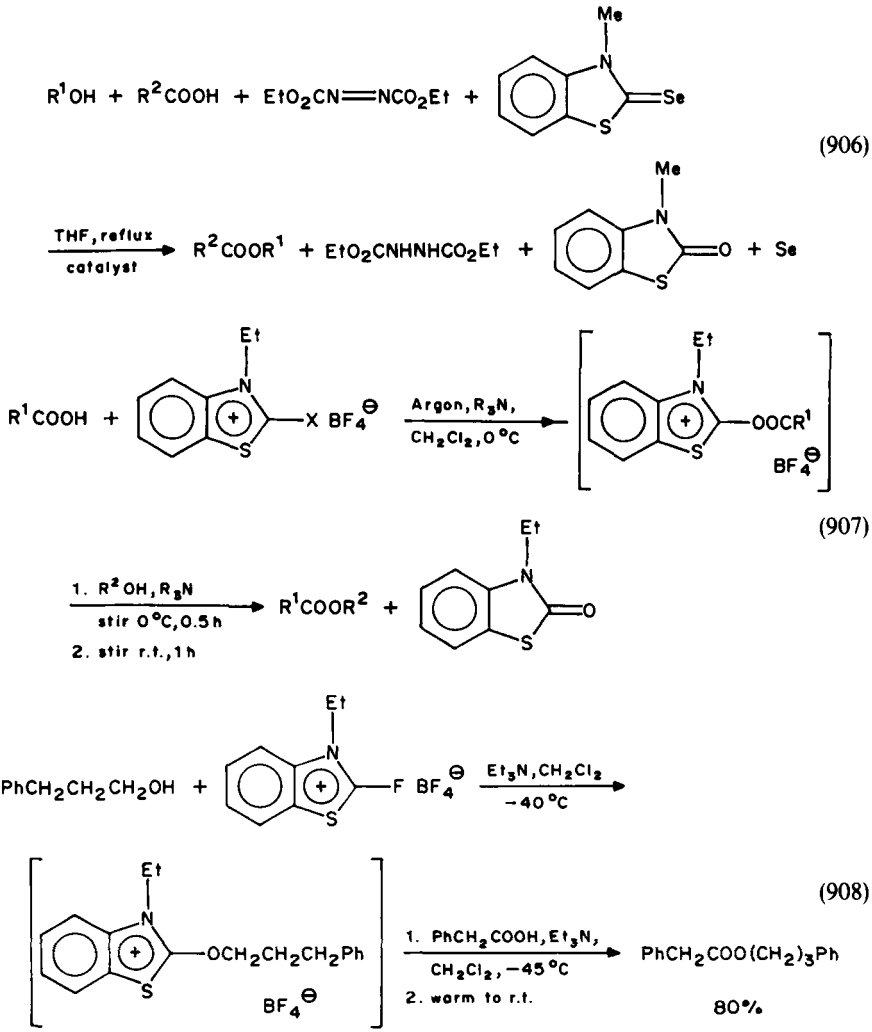


TABLE 86. Diethyl azodicarboxylate-3-methylbenzothiazole-2-selone mediated ester formation[1937]

Acid	Alcohol	Catalyst	Rx time (h)	Product	Yield (%)
PhCOOH	$PhCH_2CH_2OH$	$Me_2NC_6H_5$	9	$PhCOOCH_2CH_2Ph$	79
PhCOOH	n-C_4H_9OH	$Me_2NC_6H_5$	9	$PhCOOC_4H_9$-n	61
PhCOOH	n-$C_6H_{13}CH(Me)OH$	$Me_2NC_6H_5$	9	$PhCOOCH(Me)C_6H_{13}$-n	28
PhCOOH	Me_3COH	$Me_2NC_6H_5$	9	$PhCOOCMe_3$	0
EtCOOH	$PhCH_2CH_2OH$	$Me_2NC_6H_5$	9	$EtCOOCH_2CH_2Ph$	44
MeCH=CHCOOH	$PhCH_2CH_2OH$	$Me_2NC_6H_5$	9	$MeCH{=}CHCOOCH_2CH_2Ph$	57
$PhCH_2COOH$	$PhCH_2CH_2OH$	$Me_2NC_6H_5$	9	$PhCH_2COOCH_2CH_2Ph$	90
$PhCH_2COOH$	n-$C_6H_{13}CH(Me)OH$	$Me_2NC_6H_5$	8	$PhCH_2COOCH(Me)C_6H_{13}$-n	52[a]
$PhCH_2COOH$	n-$C_6H_{13}CH(Me)OH$	N-Methylimidazole	8	$PhCH_2COOCH(Me)C_6H_{13}$-n	55[b]
$PhCH_2COOH$	n-$C_6H_{13}CH(Me)OH$	Tetrazole	8	$PhCH_2COOCH(Me)C_6H_{13}$-n	33

[a]Product obtained with 90% retention of configuration.
[b]Product obtained with complete retention of configuration.

TABLE 87. 2-Halo-3-ethylbenzothiazolium fluoroborate mediated ester formation[1938]

Acid	Alcohol	X	Amine base	Product	Yield (%)
$PhCH_2COOH$	EtOH	Cl	$(n\text{-}Bu)_3N$	$PhCH_2COOEt$	98
$PhCH_2COOH$	$PhCH_2OH$	Cl	$(n\text{-}Bu)_3N$	$PhCH_2COOCH_2Ph$	92
$PhCH_2COOH$	PhCH(OH)Me	Cl	$(n\text{-}Bu)_3N$	$PhCH_2COOCH(Me)Ph$	92
$PhCH_2COOH$	PhOH	Cl	$(n\text{-}Bu)_3N$	$PhCH_2COOPh$	71
PhCOOH	$Ph(CH_2)_3OH$	F	Et_3N[a]	$PhCOO(CH_2)_3Ph$	71
$Ph(CH_2)_3COOH$	$Ph(CH_2)_3OH$	F	Et_3N	$Ph(CH_2)_2COO(CH_2)_3Ph$	75
PhCH(Et)COOH	$Ph(CH_2)_3OH$	F	Et_3N	$PhCH(Et)COO(CH_2)_3Ph$	73
$PhCH_2COOH$	Me_3COH	Cl	$(n\text{-}Bu)_3N$	$PhCH_2COOCMe_3$	47[b]
$PhCH_2COOH$	Me_3COH	F	Et_3N	$PhCH_2COOCMe_3$	42[b]

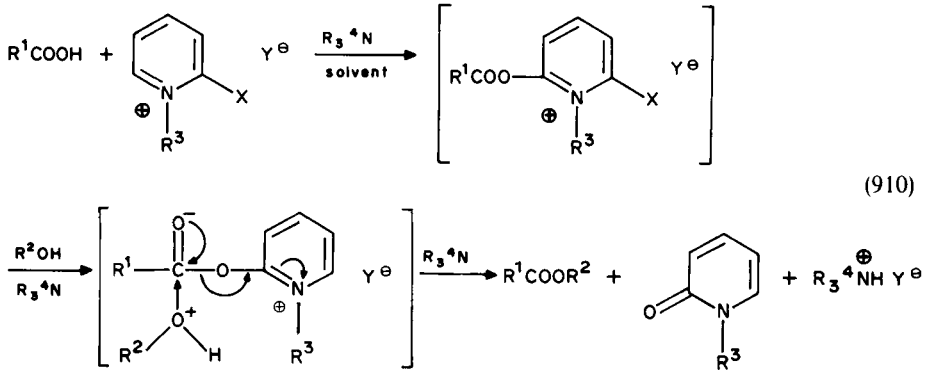
[a]The reaction was run at $-78\,^{\circ}C$.
[b]Either toluene or a mixture of toluene and methylene chloride was used as solvent.

The use of *t*-butyl isocyanide as a dehydrating agent[1939] in solution of carboxylic acids and alcohols at 20 °C and allowing the mixtures to stand for 3–9 days, affords a very mild, nonacid catalyzed preparation of carboxylic acids. This method is useful for the preparation of *t*-butyl esters, mono esters of dicarboxylic acids and amino acid esters, some examples of which are listed below (equation 909).

$$R^1COOH + R^2OH + t\text{-BuNC} \xrightarrow[3\text{-}9\text{ days}]{20\,^\circ C} [R^1COOCH{=}NBu\text{-}t] \xrightarrow{R^2OH} R^1COOR^2 + OHC\text{-}NHBu\text{-}t \quad (909)$$

Ester	Yield (%)	Ester	Yield (%)
HOOCCOOMe	36	MeCOOBu-*t*	69
$HOOCCH_2COOEt$	80	$OCHNHCH_2COOEt$	70
$HOOCCH_2COOPr\text{-}i$	66	$PhCH_2OOCNHCH(CH_2OH)COOEt$	73
$HOOCCH_2COOBu\text{-}t$	74	$PhCH_2OOCNHCH(CH_2SCOOCH_2Ph)COOEt$	98
$HOOCCH_2COOCH_2Ph$	37	$TfNHCH(CH_2Ph)COOEt$	96
$HOOC(CH_2)_3COOMe$	96	$PhCH_2OOCNHCH(CH_2CH_2CONH_2)COOMe$	76

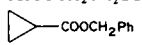
An earlier procedure[1938a,1940] which involves the reaction of equimolar amounts of a carboxylic acid and an alcohol or phenol in the presence of 1-alkyl-2-halopyridinium halide and a tertiary amine (equation 910) has been further studied[1941–1945]. The results of these studies are presented in Table 88.



(910)

The use of phosphorus-containing compounds, either alone or in combination with other reagents, as condensation reagents in reactions of carboxylic acids with alcohols to form esters, has seen a marked increase in recent years. Triphenylphosphine in the presence of triethylamine[1946] reacts with *p*-bromophenol and carboxylic acids by the mechanism shown below and the overall reaction shown in equation 911. Phosphoric

TABLE 88. Ester preparations using 1-alkyl-2-halopyridinium halides (equation 910)

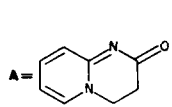
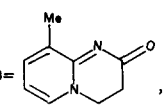
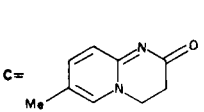
R^1	R^2	R^3	X	Amine Catalyst[a]	Y	Solvent	Temp (°C) Time (h)	Product	Yield (%)	Reference
Me	$PhCH_2$	Me	Br	$(n\text{-}Bu)_3N$	I	CH_2Cl_2	Reflux, 3	$MeCOOCH_2Ph$	80	1941
Me	$PhCH_2CH_2$	Me	Cl	$(n\text{-}Bu)_3N$	I	CH_2Cl_2	Reflux, 3	$MeCOOCH_2CH_2Ph$	74	1941
Me	$PhCH{=}CHCH_2$	Me	Br	$(n\text{-}Bu)_3N$	I	CH_2Cl_2	Reflux, 3	$MeCOOCH_2CH{=}CHPh$	80	1941
Et	$PhCH_2$	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	Reflux, 3	$EtCOOCH_2Ph$	62	1941
Et	$PhCH_2$	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	r.t., overnight	$EtCOOCH_2Ph$	71	1941
Et	$PhCH_2$	Me	Cl	$(n\text{-}Bu)_3N$	I	CH_2Cl_2	Reflux, 3	$EtCOOCH_2Ph$	39	1941
Et	$PhCH_2CH_2$	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	Reflux, 3	$EtCOOCH_2CH_2Ph$	60	1941
Et	$PhCH_2CH_2$	Me	Cl	$(n\text{-}Bu)_3N$	I	CH_2Cl_2	Reflux, 3	$EtCOOCH_2CH_2Ph$	48	1941
Et	$PhCH{=}CHCH_2$	Me	F	**A**	OTs	CH_2Cl_2	r.t., 7.5	$EtCOOCH_2CH{=}CHPh$	60	1942
n-Bu	$PhCH_2$	Me	F	**A**	OTs	CH_2Cl_2	r.t., 46	$n\text{-}BuCOOCH_2Ph$	74	1942
$n\text{-}C_8H_{17}$	$PhCH_2$	Me[b]	Cl	**B**	BF_4	CH_2Cl_2	r.t., 4	$n\text{-}C_8H_{17}COOCH_2Ph$	94	1944
$n\text{-}C_{11}H_{23}$	$PhCH_2$	Me	F	**A**	OTs	$ClCH_2CH_2Cl$	r.t., 1 then reflux, 5	$n\text{-}C_{11}H_{23}COOCH_2Ph$	42	1942
Me_2CH	$PhCH_2$	Me	Cl	**B**	I	CH_2Cl_2	r.t., 4	$Me_2CHCOOCH_2Ph$	75	1944
Me_3C	$PhCH_2$	Me	Cl	$(n\text{-}Bu)_3N$	I	CH_2Cl_2	Reflux, 3	$Me_3CCOOCH_2Ph$	31	1941
Me_3C	$PhCH_2$	Me	Cl	$(n\text{-}Bu)_3N$	I	MeC_6H_5	Reflux, 3	$Me_3CCOOCH_2Ph$	62	1941
Me_3C	Me_3C	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	Reflux, 3	$Me_3CCOOCMe_3$[c]	21	1941
Me_3C	Me_3C	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	r.t., overnight	$Me_3CCOOCMe_3$	54	1941
$ClCH_2$	$PhCH_2Et$	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	Reflux, 3	$ClCH_2COOCH_2Ph$	88	1941
$ClCH_2$	$PhCH_2CH_2$	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	Reflux, 3	$ClCH_2COOCH_2CH_2Ph$	80	1941
Cl_3C	$PhCH_2$	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	Reflux, 3	$Cl_3CCOOCH_2Ph$	40	1941
Cl_3C	$PhCH_2$	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	r.t., overnight	$Cl_3CCOOCH_2Ph$	62	1941
$MeCOCH_2CH_2$	$PhCH_2$	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	r.t., overnight	$MeCOCH_2CH_2COOCH_2Ph$	45	1941
	$PhCH_2$	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	r.t., overnight		62	1941
MeCH=CH (*trans*)	$Ph(CH_2)_3$	Et	F	CsF	BF_4	CH_2Cl_2	r.t., overnight	$MeCH{=}CHCOO(CH_2)_3Ph$	70	1943
$Me_2C{=}CH$	$Ph(CH_2)_3$	Et	F	CsF	BF_4	CH_2Cl_2	r.t., overnight	$Me_2C{=}CHCOO(CH_2)_3Ph$	70	1943
—CH(Me)CH(Me)—	Me	Et	F	CsF	BF_4	CH_2Cl_2	r.t., 1	MeOOCCH(Me)CH(Me)COOMe	70	1943
$Me(CH{=}CH)_2$	$PhCH_2$	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	r.t., overnight	$Me(CH{=}CH)_2COOCH_2Ph$	59	1941
2-Fu	$PhCH_2$	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	r.t., overnight	$2\text{-}FuCOOCH_2Ph$	97	1941
Ph	$PhCH_2$	Me	Br	$(n\text{-}Bu)_3N$	I	CH_2Cl_2	Reflux, 3	$PhCOOCH_2Ph$	80	1941
$PhCH_2$	Me	Me	Cl	**B**	I	CH_2Cl_2	r.t., 4	$PhCH_2COOMe$	90	1944
$PhCH_2$	Et	Me	Br	$(n\text{-}Bu)_3N$	I	CH_2Cl_2	Reflux, 3	$PhCH_2COOEt$	92	1941
$PhCH_2$	Me_3C	Me	Br	$(n\text{-}Bu)_3N$	I	CH_2Cl_2	Reflux, 3	$PhCH_2COOCMe_3$	70	1941
$PhCH_2$	Me_3C	Me	Br	$(n\text{-}Bu)_3N$	I	MeC_6H_5	Reflux, 3	$PhCH_2COOCMe_3$	82	1941

(*continued*)

TABLE 88. (*continued*)

R^1	R^2	R^3	X	Amine Catalyst[a]	Y	Solvent	Temp (°C) Time (h)	Product	Yield (%)	Reference
$PhCH_2$	Me_3C	Me	Br	C	I	CH_2Cl_2	r.t., 4	$PhCH_2COOCMe_3$	82	1944
$PhCH_2$	Me_3C	Me	Cl	$(n\text{-}Bu)_3N$	I	CH_2Cl_2	Reflux, 3	$PhCH_2COOCMe_3$	81	1941
$PhCH_2$	Me_3C	Me	Cl	$(n\text{-}Bu)_3N$	I	MeC_6H_5	Reflux, 3	$PhCH_2COOCMe_3$	84	1941
$PhCH_2$	Me_3C	Me	Cl	A	I	CH_2Cl_2	r.t., 8	$PhCH_2COOCMe_3$	72	1942
$PhCH_2$	Me_3C	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	r.t., overnight	$PhCH_2COOCMe_3$	78	1941
$PhCH_2$	*n*-Bu	Me	Cl	A	I	CH_2Cl_2	r.t., 3	$PhCH_2COOBu\text{-}n$	89	1942
$PhCH_2$	$n\text{-}C_6H_{13}$	Me	Cl	B	I	CH_2Cl_2	r.t., 4	$PhCH_2COOC_6H_{13}\text{-}n$	95	1944
$PhCH_2$	$n\text{-}C_9H_{19}$	Me[b]	Cl	B	BF_4	CH_2Cl_2	r.t., 4	$PhCH_2COOC_9H_{19}\text{-}n$	92	1944
$PhCH_2$	$MeCH_2CH(Me)$	Me	Cl	A	I	CH_2Cl_2	r.t., 3	$PhCH_2COOCH(Me)CH_2Me$	72	1942
$PhCH_2$	$MeCH{=}CHCH_2$	Me	Cl	A	I	CH_2Cl_2	r.t., 3	$PhCH_2COOCH_2CH{=}CHMe$	94	1942
$PhCH_2$	Ph	Me	Cl	$(n\text{-}Bu)_3N$	I	CH_2Cl_2	Reflux, 3	$PhCH_2COOPh$	90	1941
$PhCH_2$	Ph	Me	Cl	A	I	CH_2Cl_2	r.t., 3	$PhCH_2COOPh$	78	1942
$PhCH_2$	Ph	Me	Cl	B	I	CH_2Cl_2	r.t., 4	$PhCH_2COOPh$	87	1944
$PhCH_2$	$PhCH_2$	Me	Cl	Et_3N	I	CH_2Cl_2	Reflux, 3	$PhCH_2COOCH_2Ph$	98	1941
$PhCH_2$	$PhCH_2$	Me	Cl	$(n\text{-}Bu)_3N$	I	CH_2Cl_2	Reflux, 3	$PhCH_2COOCH_2Ph$	99	1941
$PhCH_2$	$PhCH_2$	Me	Cl	2,6-Dimethyl-pyridine	I	CH_2Cl_2	Reflux, 3	$PhCH_2COOCH_2Ph$	97	1941
$PhCH_2$	$PhCH_2$	Me	Cl	2-methyl pyridine	I	CH_2Cl_2	Reflux, 3	$PhCH_2COOCH_2Ph$	77	1941
$PhCH_2$	$PhCH_2$	Me	Cl	pyridine	I	CH_2Cl_2	Reflux, 3	$PhCH_2COOCH_2Ph$	62	1941
$PhCH_2$	$PhCH_2$	Me	Cl	$Et_2NC_6H_5$	I	CH_2Cl_2	Reflux, 3	$PhCH_2COOCH_2Ph$	43	1941
$PhCH_2$	$PhCH_2$	Me	Cl	$(n\text{-}Bu)_3N$	I	Et_2O	Reflux, 3	$PhCH_2COOCH_2Ph$	97	1941
$PhCH_2$	$PhCH_2$	Me	Cl	$(n\text{-}Bu)_3N$	I	THF	45–50, 3	$PhCH_2COOCH_2Ph$	97	1941
$PhCH_2$	$PhCH_2$	Me	Cl	$(n\text{-}Bu)_3N$	I	MeCN	45–50, 3	$PhCH_2COOCH_2Ph$	98	1941
$PhCH_2$	$PhCH_2$	Me	Cl	$(n\text{-}Bu)_3N$	I	DME	45–50, 3	$PhCH_2COOCH_2Ph$	98	1941
$PhCH_2$	$PhCH_2$	Me	Cl	$(n\text{-}Bu)_3N$	I	C_5H_5N	45–50, 3	$PhCH_2COOCH_2Ph$	98	1941
$PhCH_2$	$PhCH_2$	Me	Cl	$(n\text{-}Bu)_3N$	I	MeC_6H_5	45–50, 3	$PhCH_2COOCH_2Ph$	80	1941
$PhCH_2$	$PhCH_2$	Me	Cl	A	I	CH_2Cl_2	r.t., 3	$PhCH_2COOCH_2Ph$	96	1942
$PhCH_2$	$PhCH_2$	Me	Cl	B	I	CH_2Cl_2	r.t., 4	$PhCH_2COOCH_2Ph$	99	1944
$PhCH_2$	$PhCH_2$	Me	Br	$(n\text{-}Bu)_3N$	I	CH_2Cl_2	Reflux, 3	$PhCH_2COOCH_2Ph$	97	1941, 1945
$PhCH_2$	$PhCH_2CH_2$	Me	Cl	$(n\text{-}Bu)_3N$	I	CH_2Cl_2	Reflux, 3	$PhCH_2COOCH_2CH_2Ph$	93	1941
$PhCH_2$	PhCHMe	Me	Cl	$(n\text{-}Bu)_3N$	I	CH_2Cl_2	Reflux, 3	$PhCH_2COOCH(Me)Ph$	85	1941

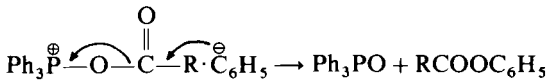
$PhCH_2$	PhCHMe	Me	Cl	$(n\text{-}Bu)_3N$	I	MeC_6H_5	Reflux, 3	$PhCH_2COOCH(Me)Ph$	88	1941
$PhCH_2$	$CH_2{=}CHCH_2$	Me	Br	**B**	I	CH_2Cl_2	r.t., 4	$PhCH_2COOCH_2CH{=}CH_2$	98	1944
$PhCH_2$	$PhCH{=}CHCH_2$	Me	Cl	**A**	I	CH_2Cl_2	r.t., 3	$PhCH_2COOCH_2CH{=}CHPh$	97	1941
$PhCH_2$	$PhCH{=}CHCH_2$	Me	Cl	**B**	I	CH_2Cl_2	r.t., 4	$PhCH_2COOCH_2CH{=}CHPh$	96	1944
$PhCH_2$	$p\text{-}Me_3CC_6H_4$	Me	Cl	**B**	I	CH_2Cl_2	r.t., 4	$PhCH_2COOC_6H_4CMe_3\text{-}p$	95	1944
$PhCH_2CH_2$	Et	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	Reflux, 3	$PhCH_2CH_2COOEt$	73	1941
$PhCH_2CH_2$	Et	Me	Cl	$(n\text{-}Bu)_3N$	I	CH_2Cl_2	Reflux, 3	$PhCH_2CH_2COOEt$	59	1941
$PhCH_2CH_2$	Ph	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	Reflux, 3	$PhCH_2CH_2COOPh$	57	1941
$PhCH_2CH_2$	Ph	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	r.t., overnight	$PhCH_2CH_2COOPh$	61	1941
$PhCH_2CH_2$	$PhCH_2$	Me	F	**A**	OTs	CH_2Cl_2	r.t., 6	$PhCH_2CH_2COOCH_2Ph$	74	1942
$PhCH_2CH_2$	$PhCH_2$	Me	Cl	$(n\text{-}Bu)_3N$	I	CH_2Cl_2	Reflux, 1	$PhCH_2CH_2COOCH_2Ph$	69	1941
$PhCH_2CH_2$	$PhCH_2$	Me	Br	$(n\text{-}Bu)_3N$	I	CH_2Cl_2	Reflux, 1	$PhCH_2CH_2COOCH_2Ph$	61	1941
$PhCH_2CH_2$	$PhCH_2$	Et	Cl	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	Reflux, 1	$PhCH_2CH_2COOCH_2Ph$	73	1941
$PhCH_2CH_2$	$PhCH_2$	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	Reflux, 1	$PhCH_2CH_2COOCH_2Ph$	82	1941
$PhCOCH_2$	$PhCH_2$	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	r.t., overnight	$PhCOCH_2COOCH_2Ph$	87	1941
$PhCH{=}CH$	Et	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	Reflux, 3	$PhCH{=}CHCOOEt$	43	1941
$PhCH{=}CH$	Et	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	r.t., overnight	$PhCH{=}CHCOOEt$	78	1941
$PhCH{=}CH$	Et	Me	Cl	$(n\text{-}Bu)_3N$	I	CH_2Cl_2	Reflux, 3	$PhCH{=}CHCOOEt$	27	1941
$PhCH{=}CH$	$PhCH_2$	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	Reflux, 3	$PhCH{=}CHCOOCH_2Ph$	71	1941
$PhCH{=}CH$	$PhCH_2$	Me	Cl	$(n\text{-}Bu)_3N$	I	CH_2Cl_2	Reflux, 3	$PhCH{=}CHCOOCH_2Ph$	62	1941
$PhC{\equiv}C$	$PhCH_2$	Et	Br	$(n\text{-}Bu)_3N$	BF_4	CH_2Cl_2	r.t., overnight	$PhC{\equiv}CCOOCH_2Ph$	85	1941
$Ph(CH_2)_3$	$Ph(CH_2)_3$	Et	F	CsF	BF_4	CH_2Cl_2	r.t., overnight	$Ph(CH_2)_3COO(CH_2)Ph$	94	1943
$Ph(CH_2)_3$	Dihydrocholesteryl	Et	F	CsF	BF_4	CH_2Cl_2	r.t., overnight	Dihydrocholesteryl-$OOC(CH_2)_3Ph$	92	1943
$p\text{-}O_2NC_6H_4$	Me	Me	Cl	**B**	I	CH_2Cl_2	r.t., 4	$p\text{-}O_2NC_6H_4COOMe$	98	1944
$p\text{-}O_2NC_6H_4$	$PhCH_2$	Me	Cl	**B**	I	CH_2Cl_2	r.t., 4	$p\text{-}O_2NC_6H_4COOCH_2Ph$	95	1944
$3,4\text{-}(O_2N)_2C_6H_3$	$p\text{-}MeOC_6H_4CH_2$	Me	Cl	**B**	I	CH_2Cl_2	r.t., 4	$3,4\text{-}(O_2N)_2C_6H_3COOCH_2C_6H_4OMe\text{-}p$	99	1944
4-Pyr	Me	Me	Cl	**B**	I	CH_2Cl_2	r.t., 4	4-PyrCOOMe	85	1944
4-Pyr	$PhCH_2$	Me	Cl	**B**	I	CH_2Cl_2	r.t., 4	4-PyrCOOCH_2Ph	95	1944
2-Pyr	Me	Me	Cl	**B**	I	CH_2Cl_2	r.t., 4	2-PyrCOOMe	85	1944

[a] **A**=  , **B**=  , **C**= 

[b] Pyridinium salt used contained a 5-nitro group.

anhydride[1947,1948] reacts with the substrate alcohols to produce alkylphosphoric ester intermediates which then react with carboxylic acids (equation 912) to produce esters. This method is especially effective[1947,1948] in esterifying amic and anilic acids (equation 913), although in some cases imides are the only products formed. Methyl (*n*-propyl) phenyl phosphine in combination with diethyl azodicarboxylate effects condensation[1949] of *p*-nitrophenol and benzoic acid (equation 914) or (*E*)-4-(*t*-butyl) cyclohexanol and *p*-hydroxybenzoic acid (equation 915) to produce the corresponding esters.

$$p\text{-}BrC_6H_4OH + Ph_3P \rightarrow Ph_3\overset{\oplus}{P}OC_6H_5 \cdot Br^{\ominus} \xrightarrow[(Et_3N \cdot HBr)]{RCOOH,\ Et_3N} \tag{911}$$



$$Ph_3\overset{\oplus}{P}-O-\overset{O}{\overset{\|}{C}}-R\cdot\overset{\ominus}{C}_6H_5 \longrightarrow Ph_3PO + RCOOC_6H_5$$

overall reaction:

$$p\text{-}BrC_6H_4OH + RCOOH \xrightarrow[\text{heat, 4 h}]{Ph_3P,\ Et_3N}$$

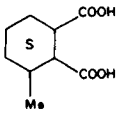
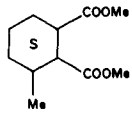
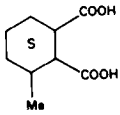
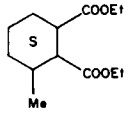
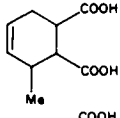
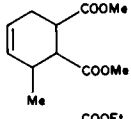
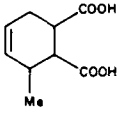
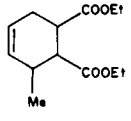
$$RCOOC_6H_4Br\text{-}p + RCOOPh + Et_3N \cdot HBr + Ph_3PO$$

R	Rx temp. (°C)	Ph ester % yield	*p*-BrPh ester % yield
Me	200	50	0
Me	170	46	13
Me[a]	200	0	0
n-Pr	200	62	4
Ph	200	84	0
Ph	170	62	12
Ph[b]	170	9	21
p-ClC_6H_4	200	64	0
p-ClC_6H_4	170	54	4
o-ClC_6H_4	200	40	0
p-Tol	200	75	14
p-An	200	62	5
p-$O_2NC_6H_4$	200	0	0
PhCH=CH	200	58	5

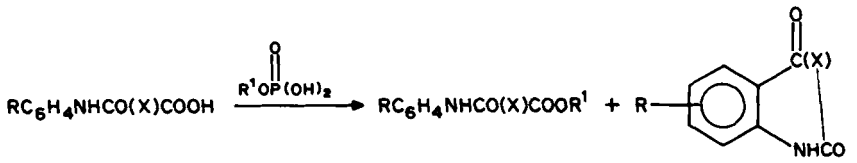
[a] Reaction run in the absence of NEt_3.
[b] Pyridine was used in place of NEt_3.

$$ROH + P_4O_{10} \rightarrow [ROP(OH)_2 + (RO)_2POH] \xrightarrow[\substack{\text{reflux}\\ 3\text{ h}}]{R^1COOH} R^1COOR \tag{912}$$

Carboxylic acid R^1COOH	R	Product	Yield (%)
MeCOOH	Me	MeCOOMe	90
MeCOOH	Et	MeCOOEt	56
EtCOOH	Me	EtCOOMe	86

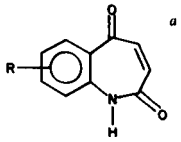
Carboxylic acid R^1COOH	R	Product	Yield (%)
EtCOOH	Et	EtCOOEt	66
n-PrCOOH	Me	*n*-PrCOOMe	80
n-PrCOOH	Et	*n*-PrCOOEt	66
Me_2CHCH_2COOH	Me	Me_2CHCH_2COOMe	70
Me_2CHCH_2COOH	Et	Me_2CHCH_2COOEt	72
$PhCH_2COOH$	Me	$PhCH_2COOMe$	89
$PhCH_2COOH$	Et	$PhCH_2COOEt$	86
HOOCCOOH	Me	MeOOCCOOMe	95
HOOCCOOH	Et	EtOOCCOOEt	68
$HOOC(CH_2)_2COOH$	Me[a]	$MeOOC(CH_2)_2COOMe$	60
$HOOC(CH_2)_2COOH$	Et[a]	$EtOOC(CH_2)_2COOEt$	63
MeCH=CHCOOH(*trans*)	Me	MeCH=CHCOOMe	70
MeCH=CHCOOH(*trans*)	Et	MeCH=CHCOOEt	68
PhCH=CHCOOH(*cis*)	Me	PhCH=CHCOOMe	78
PhCH=CHCOOH(*cis*)	Et	PhCH=CHCOOEt	73
HOOCCH=CHCOOH(*cis*)	Me[b]	MeOOCCH=CHCOOMe	73
HOOCCH=CHCOOH(*cis*)	Et[b]	EtOOCCH=CHCOOEt	70
HOOCCH=C(Me)COOH(*cis*)	Me[c]	MeOOCCH=C(Me)COOMe	68
HOOCCH=C(Me)COOH(*cis*)	Et[c]	EtOOCCH=C(Me)COOEt	65
HOOCCH=CHCOOH(*trans*)	Me	MeOOCCH=CHCOOMe	72
HOOCCH=CHCOOH(*trans*)	Et	EtOOCCH=CHCOOEt	60
$ClCH_2COOH$	Me	$ClCH_2COOMe$	78
$ClCH_2COOH$	Et	$ClCH_2COOEt$	90
H_2NCH_2COOH	Me	H_2NCH_2COOMe	65
H_2NCH_2COOH	Et	H_2NCH_2COOEt	90
PhCOOH	Me	PhCOOMe	70
PhCOOH	Et	PhCOOEt	24
$3,5\text{-}(O_2N)_2C_6H_3COOH$	Me	$3,5\text{-}(O_2N)_2C_6H_3COOMe$	36
$3,5\text{-}(O_2N)_2C_6H_3COOH$	Et	$3,5\text{-}(O_2N)_2C_6H_3COOEt$	30
	Me		71
	Et		85
	Me		73
	Et		79

[a] Procedure requires stirring at room temperature for 4 hours; reflux is not required.
[b] A mixture of esters was obtained in each case with 16% *trans* and 84% *cis*.
[c] The *cis* isomer only is obtained in each case.



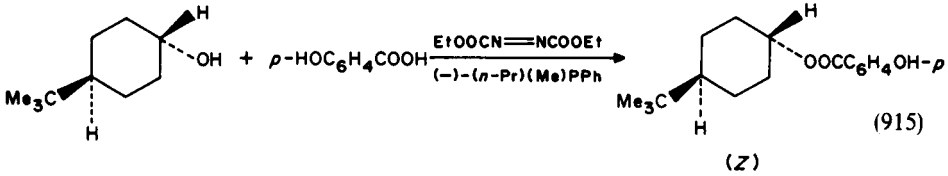
(913)

Acid	R^1	Product	Yield (%)
$RC_6H_4NHCOCH{=}CHCOOH$		$RC_6H_4NHCOCH{=}CHCOOR^1$	
R = *o*-Me(*trans*)	Me		68
R = *p*-Me(*trans*)	Me		67
R = *o*-MeO(*trans*)	Me		64
R = *p*-MeO(*trans*)	Me		65
R = *p*-Cl(*trans*)	Me		70
R = *o*-NO_2(*cis*)	Me		85
R = *o*-NO_2(*cis*)	Et		78
R = *o*-NO_2(*trans*)	Me		85
R = *o*-NO_2(*trans*)	Et		80
R = *o*-NO_2(*trans*)	*i*-Pr		—
R = *o*-NO_2(*trans*)	*n*-Pr		—
R = *o*-NO_2(*trans*)	*n*-Bu		—
R = *o*-NO_2(*trans*)	*c*-Hex		—
R = *m*-NO_2(*cis*)	Me		87
R = *m*-NO_2(*cis*)	Et		77
R = *m*-NO_2(*trans*)	Me		84
R = *m*-NO_2(*trans*)	Et		78
R = *p*-NO_2(*cis*)	Me		89
R = *p*-NO_2(*cis*)	Et		78
R = *p*-NO_2(*trans*)	Me		87
R = *p*-NO_2(*trans*)	Et		80
R = 2-NO_2 and 4-MeO (*cis*)	Me		88
R = 2-NO_2 and 4-MeO(*cis*)	Et		78
R = 2-NO_2 and 4-MeO(*trans*)	Me		89
R = 2-NO_2 and 4-MeO(*trans*)	Et		80
R = 2-NO_2 and 4-Me(*cis*)	Me		87
R = 2-NO_2 and 4-Me(*trans*)	Me		85
R = 2-NO_2 and 4-Me(*trans*)	Et		78
$RC_6H_4NHCO(CH_2)_2COOH$	Me	$RC_6H_4NHCO(CH_2)_2COOMe$	
R = *o*-Me			50
R = *p*-Me			68
R = *o*-MeO			62
R = *p*-MeO			80
R = *p*-Cl			68
R = *o*-NO_2			50
R = *m*-NO_2			72
R = *p*-NO_2			66
R = 2-NO_2 and 4-MeO			70
R = 2-NO_2 and 4-Me			80

Acid	Product	Yield (%)
$RC_6H_4NHCOCH{=}CHCOOH$ R = *o*-Me(*cis*) R = *p*-Me(*cis*) R = *o*-MeO(*cis*) R = *p*-MeO(*cis*)	 [a]	

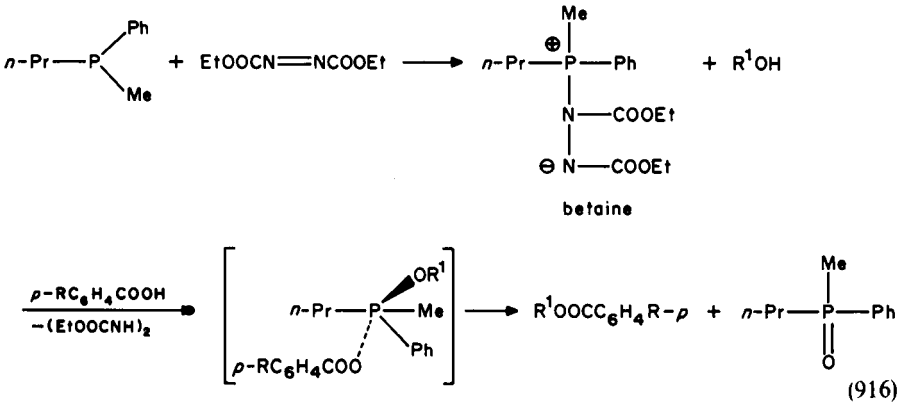
[a]Yields for these products not reported.

$$PhCOOH + p\text{-}HOC_6H_4NO_2 \xrightarrow[(-)\text{-}(n\text{-Pr})(Me)PhP]{EtOOCN{=}NCOOEt} p\text{-}O_2NC_6H_4OOCPh + EtOOCNHNHCOOEt + (\pm)\text{-}(n\text{-Pr})PO(Me)Ph \quad (914)$$



(915)

The reaction proceeds via formation of a betaine which deprotonates the phenol and the carboxylic acid to produce diethyl hydrazinedicarboxylate and a pentavalent phosphorous intermediate, which then decomposes to the ester and phosphine oxide (equation 916). Phosphoranes such as bis (2,2,2-trifluoroethoxy) triphenylphosporane[1950] (equation 917) and diethoxyvinylidenetriphenylphosphorane[1951] (equation 918) are also effective condensing agents. With the latter reagent method A required the addition of the acid in tetrahydrofuran, ether or benzene to the phosphorane in either one of the same three solvents, while method B entailed the reverse addition of the phosphorane in



(916)

tetrahydrofuran to the acid also in tetrahydrofuran. A variety of phosphates have been used, including *N,N*-dimethylphosphoramide dichloride or phenyl dichlorophosphate[1952] (equation 919), diethyl phosphorocyanidate[1953], which catalyzes the esterification of carboxylic acids with alcohols (equation 920) and also acts as a reagent itself (equation 921), and polyphosphate ester[1954] (equation 922). Dimethylchlorothiophosphorane has been reported[1955] to be an effective condensing agent for a variety of carboxylic acids and alcohols, including *t*-butoxycarbonyltryptophan and methanol (equation 923).

$$Ph_3P(OCH_2CF_3)_2 + RCOOH \xrightarrow[\substack{r.t.\\ -CF_3CH_2OH}]{CH_2Cl_2} \left[Ph_3P(OOCR)(OCH_2CF_3) \right] \xrightarrow{-Ph_3P=O} RCOOCH_2CF_3 \quad (917)$$

R =	Ph	*n*-Pr	*n*-Bu
% Yield =	82	85	80

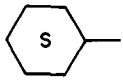
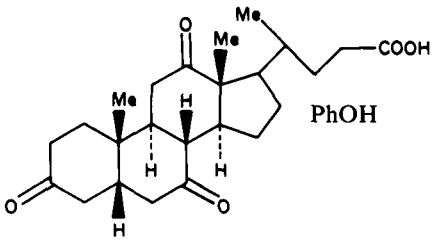
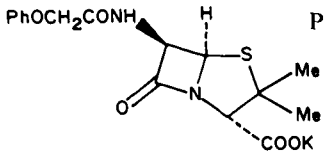
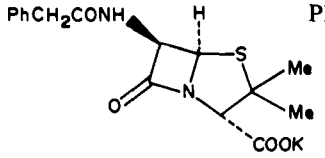
$$Ph_3\overset{\oplus}{P}\overset{\ominus}{C}{=}C(OEt)_2 + RCOOH \xrightarrow[3\,h]{r.t.,\,stir} RCOOEt \quad (918)$$

Acid	Method	Yield (%)
n-$C_5H_{11}COOH$	A	78
t-C_4H_9COOH	A	63
MeCH=CHCOOH(*trans*)	B	33
MeCH=CH—CH=CHCOOH(*trans, trans*)	B	82
PhCOOH	A	77
$PhCH_2COOH$	B	32
p-$O_2NC_6H_4COOH$	B	70
o-$H_2NC_6H_4COOH$	B	26
PhCH=CHCOOH(*trans*)	B	83
$HOOC(CH_2)_2COOH$	A	76

$$RCOOH + R^1OH \xrightarrow[2.\ r.t.,\,stir,\,Ar,\,16\,h]{1.\ C_5H_5N,\,0\,^\circ C,\,reagent\ A\ or\ B} RCOOR^1 \quad (919)$$

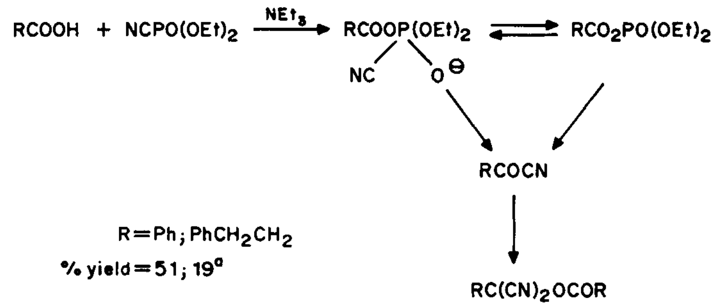
reagents: A = Me_2NPOCl_2 B = $PhOPOCl_2$

		Isolated % yield using reagent	
RCOOH	R^1OH	A	B
$PhOCH_2COOH$	$PhOCH_2CH_2OH$	82	88
$PhOCH_2COOH$	Me_3COH	89	94
$PhOCH_2COOH$	*p*-Cyclohexylcyclohexanol	76	84
$PhOCH_2COOH$	EtOH	84	97

RCOOH	R^1OH	Isolated % yield using reagent A	B
	$Ph(CH_2)_3OH$	70	81
PhOCH(Me)COOH	EtOH	83	92
PhOCH(Me)COOH	MeOH	84	85
PhOCH(Me)COOH	$PhCH_2OH$	96	95
PhOCH(Me)COOH	Me_3COH	84	90
$CH_2=CH(CH_2)_8COOH$	$CH_2=CHCH_2OH$	73	77
$EtOCH_2COOH$	PhOH	96	98
	PhOH	78	88
	$PhCH_2OH$	88	65
	PhOH	84	60

$$RCOOH + R^1OH \xrightarrow[NEt_3,\ -15\,^\circ C \text{ to r.t.}]{NCP(O)(OEt)_2} RCOOR^1 \qquad (920)$$

R	R^1	Product	% Yield
Ph	Me	PhCOOMe	35
Ph	Et	PhCOOEt	56
Ph	*i*-Pr	PhCOOPr-*i*	47
$Ph(CH_2)_2$	Me	$Ph(CH_2)_2COOMe$	52
$Ph(CH_2)_2$	*i*-Pr	$Ph(CH_2)_2COOPr$-*i*	28



(921)

^{a}Plus 18% *trans* and 5.5% *cis* of $PhCH_2CH{=}C(CN)OC(O)CH_2CH_2Ph$.

$$RCOOH + p\text{-}O_2NC_6H_4OH \xrightarrow[\text{reflux 45 min}]{\text{PPE, CHCl}_3,} RCOOC_6H_4NO_2\text{-}p \quad (922)$$

80–86%

$R = Me, n\text{-}Pr, n\text{-}C_7H_{15}, n\text{-}C_{11}H_{23}, n\text{-}C_{15}H_{31}$

$$\text{3-IndolylCH}_2\text{CH(NHCOOCMe}_3\text{)COOH} + \text{Cl—P(=S)(Me)—Me} \xrightarrow[\text{2. MeOH, imidazole, 0 °C, stir 1 h; 3. stir r.t. overnight}]{\text{1. Et}_3\text{N, CHCl}_3\text{, stir 0 °C, 1 h}} \text{3-IndolylCH}_2\text{CH(NHCOOCMe}_3\text{)COOMe} \quad (923)$$

99%

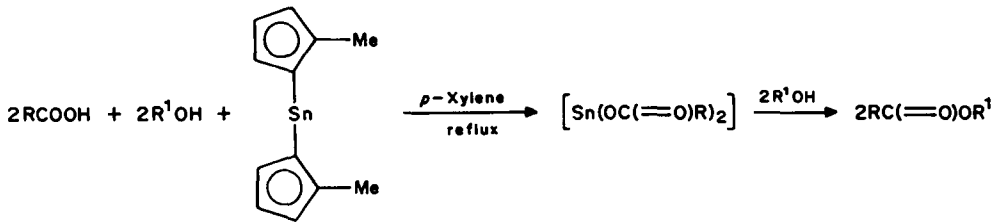
Several recent examples of esterification reactions utilize rather novel condensing agents. Three examples of the use of tin compounds to catalyze reactions of carboxylic acids and alcohols have been published[1956–1958] and have included the use of tin chloride[1956] (equation 924), dibutyl tin oxide[1957] (equation 925) and 1,1′-dimethylstannocene[1958] (equation 926). Tetra(*n*-butoxy)titanium has been reported[1959] to catalyze the formation of macrocyclic diesters from the condensation of dibasic acids with

$$n\text{-}C_5H_{11}COOH + C(CH_2OH)_4 \xrightarrow[\text{210–200 °C, 5 h}]{\text{SnCl}_2\text{, KOH}} C(CH_2OC({=}O)C_5H_{11}\text{-}n)_4 \quad (924)$$

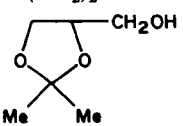
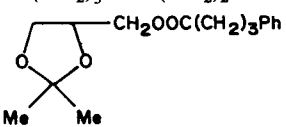
$$p\text{-}HOC_6H_4COOH + PhCH_2OH \xrightarrow[\text{N}_2\text{, 200 °C, 6 h}]{(n\text{-Bu})_2\text{SnO}} p\text{-}HOC_6H_4COOCH_2Ph \quad (925)$$

94.7%

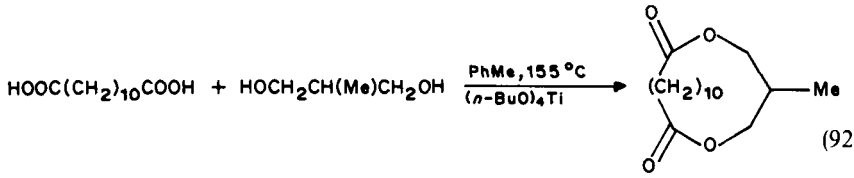
other catalysts also used: $(n\text{-}Bu)_2Sn(OAc)_2$, $(n\text{-}Bu)_3SnCl$, $(n\text{-}Bu)_4Sn$, dibutyltin dilaurate and $Ti(OCHMe_2)_4$



(926)

Acid	Alcohol	Reflux time (h)	Product	Yield (%)
Me_3CCOOH	$Ph(CH_2)_3OH$	6	$Me_3CCOO(CH_2)_3Ph$	80
$Cl_2CHCOOH$	$Ph(CH_2)_3OH$	3	$Cl_2CHCOO(CH_2)_3Ph$	74
$Cl(CH_2)_2COOH$	$Ph(CH_2)_3OH$	4	$Cl(CH_2)_2COO(CH_2)_3Ph$	78
$MeCO(CH_2)_2COOH$	$Ph(CH_2)_3OH$	3	$MeCO(CH_2)_2COO(CH_2)_3Ph$	74
$Me(CH{=}CH)_2COOH$	$Ph(CH_2)_3OH$	3	$Me(CH{=}CH)_2COO(CH_2)_3Ph$	76
PhCOOH	$Ph(CH_2)_3OH$	3	$PhCOO(CH_2)_3Ph$	81
PhCH(Et)COOH	$Ph(CH_2)_3OH$	3	$PhCH(Et)COO(CH_2)_3Ph$	85
PhCH(Et)COOH	$Ph(CH_2)_2CH(Me)OH$	9	$PhCH(Et)COOCH(Me)(CH_2)_2Ph$	79
$Ph(CH_2)_3COOH$	$Ph(CH_2)_3OH$	3	$Ph(CH_2)_3COO(CH_2)_3Ph$	86
$Ph(CH_2)_3COOH$	$Ph(CH_2)_2CH(Me)OH$	6	$Ph(CH_2)_3COOCH(Me)(CH_2)_2Ph$	80
$Ph(CH_2)_3COOH$	$Cl(CH_2)_2OH$	3	$Ph(CH_2)_3COO(CH_2)_2Cl$	75
$Ph(CH_2)_3COOH$		4		75

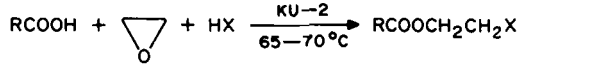
2-methyl 1,3-dihydroxypropane (equation 927). A study of the catalytic ability of chlorosilanes in esterification reactions has shown[1960] that esters may be prepared in 37–98% yield under mild conditions using these reagents (equation 928).



(927)

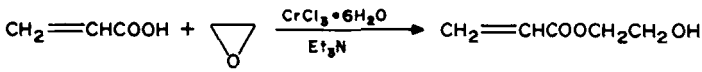
Although the condensation of a carboxylic acid with an alcohol is the most common synthetic approach to the preparation of esters, substrates containing other functional groups have replaced alcohols in this procedure. The functional groups used have included oxiranes, ethers, acetals, *ortho* esters, carbonates, chloroformates and lactams, and the reports of their use in the preparation of esters from carboxylic acids are described in this section.

Three reports of the use of oxiranes in the preparation of esters from carboxylic acids appear in the recent literature, and all three reports utilize different condensing agents to catalyze the reaction. Condensation of carboxylic acids with ethylene oxide in the presence of a hydrogen halide at 65–70 °C has been catalyzed by KU-2 to produce[1961] the corresponding 2-haloethyl esters in 62–91% yield (equation 929). Chromyl chloride, acetylacetonate or oxide and an amine has been reported[1962] to catalyze the esterification of acrylic acid with ethylene oxide (equation 930) to produce the corresponding β-hydroxy alkyl ester. Finally, the reaction of oxiranes with carboxylic acids in the presence of triphenylphosphine–carbon tetrachloride (equations 931 and 932) has been reported[1963] to produce *cis*-enol esters. The mechanism of this reaction is reported[1963] to involve nucleophilic attack of the oxirane on the acyloxytriphenylphosphonium salt produced from reaction of the triphenylphosphine–carbon tetrachloride complex with the carboxylic acid.

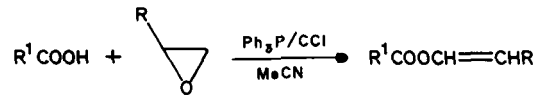


(929)

R = C_1–C_8, *n*-alkyl, $ClCH_2$, CCl_3, $ClCH_2CH_2$, 3-cyclohexen-1-yl
X = Cl, Br

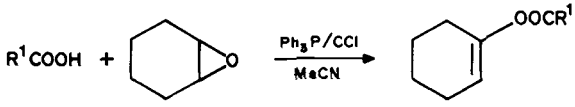


(930)



(931)

R = Ph, Et
R^1 = alkyl or aryl



(932)

R^1 = alkyl or aryl

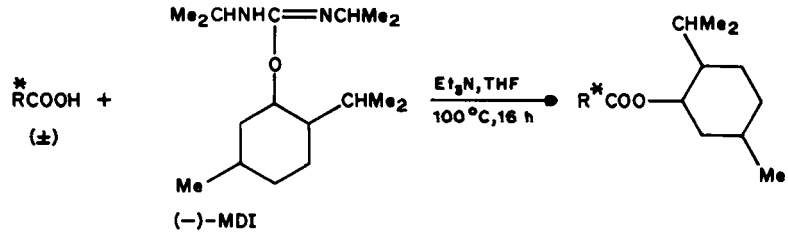
$$RCOOH + R^1OH + R^2{}_nSiCl_{4-n} \xrightarrow[\text{stand r.t.}]{\text{solvent}} [R^2{}_nCl_{3-n}SiOR^1] \xrightarrow{RCOOH} RCOOR^1 \quad (928)$$

R	R^1	Chlorosilane	Solvent	Rx time	Product	Yield (%)
Me	Me	Me_3SiCl	2-MeTHF	15–100 min[a]	MeCOOMe	72–97[a]
Me	Me	Me_2SiCl_2	2-MeTHF	—	MeCOOMe	98
Me	Me	$MeSiCl_3$	2-MeTHF	—	MeCOOMe	97
Me	Me	$SiCl_4$	2-MeTHF	—	MeCOOMe	96
Et	Me	Me_3SiCl	2-MeTHF	15 min	EtCOOMe	95
Et	Me	Me_3SiCl	2-MeTHF	100 h	EtCOOMe	93
Me_2CH	Me	Me_3SiCl	THF	15 min	$Me_2CHCOOMe$	98
Me_3C	Me	Me_3SiCl	THF	15 min	$Me_3CCOOMe$	91
Me_3C	Me_2CHCH_2	Me_3SiCl	2-MeTHF	15 min	$Me_3CCOOCH_2CHMe_2$	90
Me	Et	Me_3SiCl	2-MeTHF	15 min	MeCOOEt	92
Me	$CH_2{=}CHCH_2$	Me_3SiCl	2-MeTHF	15 min	$MeCOOCH_2CH{=}CH_2$	92
Me	Me_2CH	Me_3SiCl	2-MeTHF	15 min	$MeCOOCHMe_2$	37
Me	Me_2CH	Me_3SiCl	2-MeTHF	24 h	$MeCOOCHMe_2$	93
Me	EtMeCH	Me_3SiCl	2-MeTHF	48 h	MeCOOCHMeEt	95
Me	*c*-C_6H_{11}	Me_2SiCl_2	*n*-$C_{11}H_{24}$	48 h	$MeCOOC_6H_{11}$-*c*	81

[a]Depending upon the ratio of chlorosilane to acid used.

The use of ethers in place of alcohols in the esterification of carboxylic acids is illustrated by the preparation of methyl propionate from propionic acid and *t*-butyl methyl ether in the presence of the cation exchanger Ostion KS in its acid form[1964] (equation 933). A second example is illustrated[1965] by the use of *O*-[(−)-menthyl]*N*,*N*′-diisopropylisourea in the esterification of racemic mixtures of naphthoxylacetic and mandelic acids (equation 934) to produce their corresponding diastereomeric menthyl esters.

$$EtCOOH + MeOCMe_3 \xrightarrow[\text{MeOH, autoclave}\ 105\,^\circ C,\ 4\,h]{\text{Ostion KS}} EtCOOMe \qquad (933)$$

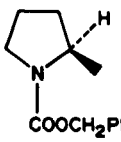
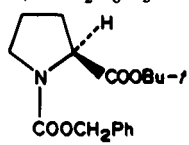


R = 1-NaphOCH$_2$*CH(OH), C$_6$H$_5$*CH(OH) (934)

By refluxing carboxylic acids with the diethyl acetal of formaldehyde in the presence of sulfuric acid[1966], the corresponding ethyl ester of the carboxylic acid is prepared (equation 935) in good yield, while refluxing four equivalents of *N*,*N*-dimethylforamide di-*t*-butyl acetal with one equivalent of carboxylic acid produces 55–83% yields of the corresponding *t*-butyl esters[1967] (equation 936).

$$PhCOOH + H_2C(OEt)_2 \xrightarrow[\text{reflux}]{H_2SO_4} PhCOOEt \quad 85\% \qquad (935)$$

$$RCOOH + (t\text{-}BuO)_2CHNMe_2 \xrightarrow[MeC_6H_5,\ 75\text{–}80\,^\circ C,\ 20\,min]{C_6H_6,\ 80\,^\circ C,\ 20\,min\ \text{or}} RCOOBu\text{-}t \qquad (936)$$

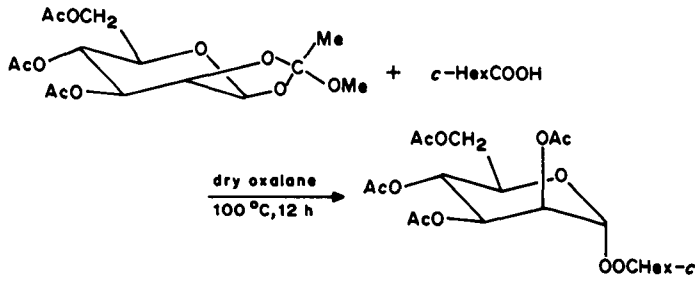
R	Product	Yield (%)
$Me(CH_2)_2CH{=}CH$	$Me(CH_2)_2CH{=}CHCOOBu\text{-}t$	55
$Me(CH_2)_4C{\equiv}C$	$Me(CH_2)_4C{\equiv}CCOOBu\text{-}t$	83
$MeCO(CH_2)_2$	$MeCO(CH_2)_2COOBu\text{-}t$	74
Ph	$PhCOOBu\text{-}t$	77
$p\text{-}O_2NC_6H_4$	$p\text{-}O_2NC_6H_4COOBu\text{-}t$	78
$p\text{-}MeOC_6H_4$	$p\text{-}MeOC_6H_4COOBu\text{-}t$	72
$o\text{-}HOC_6H_4$	$o\text{-}HOC_6H_4COOBu\text{-}t$	75
$2,6\text{-}Me_2C_6H_3$	$2,6\text{-}Me_2C_6H_3COOBu\text{-}t$	82
		79
$(CH_2)_2(COOH)_2$	$t\text{-}BuOOC(CH_2)_2COOBu\text{-}t$	83
$(CH_2)_3(COOH)_2$	$t\text{-}BuOOC(CH_2)_3COOBu\text{-}t$	81

At least two reports of the use of ortho esters in place of alcohols in the esterification of carboxylic acids have appeared in the recent literature. The first describes the preparation[1968] of ethyl 3,3-dimethylpenten-4-oate from the precursor carboxylic acid by reaction with ethyl orthoacetate in the presence of phosphoric acid at 150 °C (equation 937).

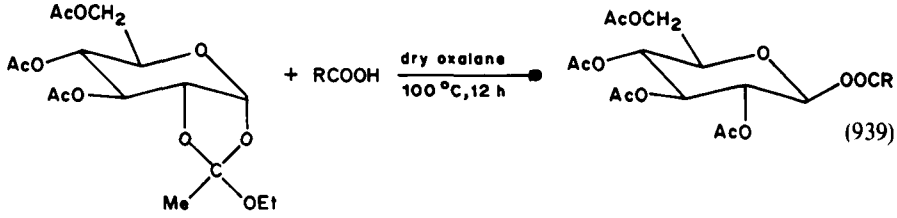
$$CH_2{=}CHCMe_2CH_2COOH + MeC(OEt)_3 \xrightarrow[150\,^\circ C,\ 1\,h]{H_3PO_4} CH_2{=}CHCMe_2CH_2COOEt \quad (937)$$

80%

The second report[1969] involves the synthesis of 1-*O*-acylaldoses of inverted configuration by reaction of carboxylic acids with either 3,4,6-tri-*O*-acetyl-(1,2-alkoxyethylidene)-β-D-mannopyranose (equation 938) or α-D-glucopyranose (equation 939).



(938)



(939)

Acid	% Yield of 1-*O*-acylaldose
c-HexCOOH	66
o-$MeCOOC_6H_4COOH$	48
Me_3CCOOH	34
$MeCH_2COOH$	49
2-PyrCOOH	25
PhCOOH	57

Although di-2-pyridyl carbonate (2-DPC) can replace the analagous alcohols in the esterification of carboxylic acids[1970] (equation 940), it has been reported[1970] to be more effective as a coupling agent in the esterification of carboxylic acids with *N*-hydroxysuccinimide, *N*-hydroxyphthalimide, 1-hydroxybenzotriazole and *p*-hydroxyphenol (equation 941).

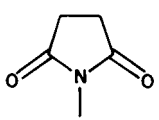
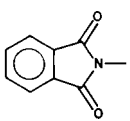
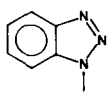
$$RCOOH + 2\text{-PyrOC(O)OPyr-2(2-DPC)} \xrightarrow[\text{r.t., 1 h}]{\text{4-PyrNMe}_2,\ CH_2Cl_2} 2\text{-PyrOCOR} \qquad (940)$$

R =	Me	Ph	$Me_3CO{-}\overset{\overset{O}{\|}}{C}{-}NHCH(CH_2CHMe_2)$	$Me_3CO{-}\overset{\overset{O}{\|}}{C}{-}NHCH(Me)$
% Yield =	90	85	81	72

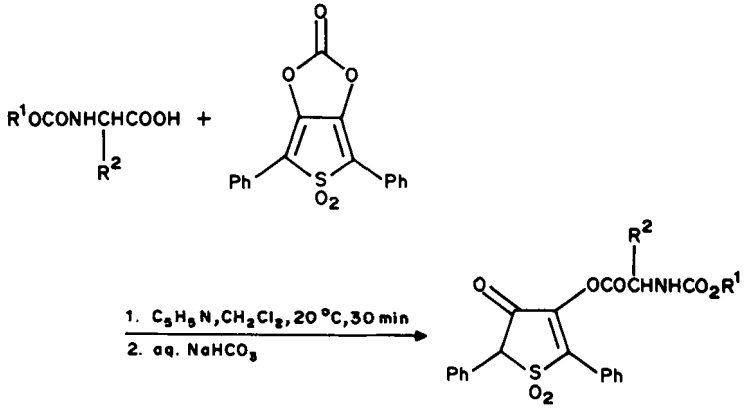
$$RCOOH + R^1OH \xrightarrow[\text{4-PyrNMe}_2,\ \text{r.t. 1 h}]{\text{2-DPC, } CH_2Cl_2} RCOOR^1 + 2\text{-PyrOH} \qquad (941)$$

R	R^{1a}	Product[a]	Yield (%)
Me	N-SI	MeCOO(N-SI)	86
Ph	N-SI	PhCOO(N-SI)	92
$PhCH_2OOCNHCH(CH_2CHMe_2)$	N-SI	$PhCH_2OOCNHCH(CH_2CHMe_2)COO(N\text{-SI})$	85
$PhCH_2OOCNHCH(CH_2Ph)$	N-SI	$PhCH_2OOCNHCH(CH_2Ph)COO(N\text{-SI})$	87
$Me_3COOCNHCH(Me)$	N-SI	$Me_3COONHCH(Me)COO(N\text{-SI})$	76

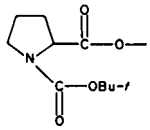
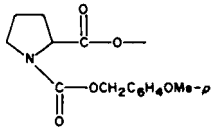
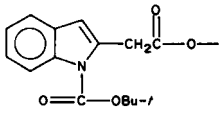
Ph	N-PHI	PhCOO(N-PHI)	88
$PhCH_2OOCNHCHCH_2CHMe_2$	N-PHI	$PhCH_2OOCNHCHCOO(N\text{-}PHI)$ H_2CHMe_2C	88
Ph	1-BTR	(1-BTR)OOCPh	90
Me	1-BTR	(1-BTR)OOCMe	85
$PhCH_2OOCNHCHCH_2Ph$	1-BTR	$(1\text{-BTR})OOCCHNHCOOCH_2Ph$ CH_2Ph	88
Ph	$p\text{-}HOC_6H_4NO_2$	$PhCOOC_6H_4NO_2\text{-}p$	89
$PhCH_2OOCNHCHCH_2CMe_2$	$p\text{-}HOC_6H_4NO_2$	$PhCH_2OOCNHCHCOOC_6H_4NO_2\text{-}p$ CH_2CHMe_2	85
$Me_3COOCNHCHMe$	$p\text{-}HOC_6H_4NO_2$	$Me_3COOCNHCHCOOC_6H_4NO_2\text{-}p$ Me	78

[a] N—SI=  ≡(*N*-succinimido), N—PHI=  ≡(*N*-phthalimido), 1-BTR=  ≡(1-benzotriazolyl).

Another carbonate which has been used to prepare[1971] activated *N*-*t*-butoxycarbonyl amino acid esters is 4,6-diphenylthieno-[3,4-*d*]-[1,3]-dioxol-2-one 5,5-dioxide (equation 942).



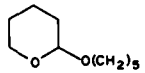
(942)

R^1	R^2	Yield (%)
t-Bu	Me	82
t-Bu	CH_2SCOPh	90
t-Bu	H	72
t-Bu	Me_2CHCH_2	83
t-Bu	$PhCH_2$	84
t-Bu	CH_2OCOPh	87
t-Bu	Me_2CH	87
p-$MeOC_6H_4CH_2$	Me_2CHCH_2	85
		92
		76
		72

Simple aliphatic carboxylic esters have been prepared[1972] in high yields by the reaction of carboxylic acids with equimolar amounts of chloroformates and triethylamine in the presence of a catalytic amount of 4-(dimethylamino)pyridine. If the amount of the 4-(dimethylamino)pyridine catalyst is increased, then the amount of acid anhydride and carbonate normally formed during esterification of aromatic acids can be reduced to the point where the ester products from these acids can be obtained in satisfactory yields

(equation 943). With 2,2,2-trichloroethyl chloroformate (equation 944), two different methods of reagent addition were used[1972]: Method A involved the addition of the 4-(dimethylamino)pyridine catalyst into an equimolar mixture of the acid, the chloroformate and triethylamine, while Method B involved the addition of the chloroformate into a reaction mixture of the acid, triethylamine and the (dimethylamino)pyridine catalyst.

$$RCOOH + Cl{-}\overset{\overset{O}{\|}}{C}{-}OR^1 + Et_3N \xrightarrow[CH_2Cl_2,\ 0\,^\circ C]{4\text{-}PyrNMe_2} RCOOR^1 \qquad (943)$$

R	R^1	Rx time (h)	Yield (%)
n-C_7H_{15}	Me	0.25	98
n-C_7H_{15}	Et	0.5	95
n-C_7H_{15}	$PhCH_2$	0.5	97
n-C_7H_{15}	Me_2CH	0.25	96
n-C_7H_{15}	*i*-Pr_2CH	1	96
n-C_7H_{15}	*p*-$O_2NC_6H_4$	0.25	97
$PhCH_2$	Me	1	94
$PhCH_2$	$PhCH_2$	1	94
Me_2CH	Et	0.25	92
Me_2CH	$PhCH_2$	0.25	89
Me_2CH	*i*-Pr_2CH	1	93
Me_2CH	*p*-$O_2NC_6H_4$	0.5	94
c-Hex	Et	1	92
c-Hex	$PhCH_2$	1	92
c-Hex	*i*-Pr	0.25	96
Ph_2CH	Me	0.5	98
Ph_2CH	Et	0.25	93
Ph_2CH	$PhCH_2$	0.25	95
Ph_2CH	*i*-Pr	0.25	95
Ph	Et	0.5–3	56–91[a]
Ph	*p*-$O_2NC_6H_4$	0.5	88
p-ClC_6H_4	Et	0.5–2	76–89[a]
p-ClC_6H_4	*p*-$O_2NC_6H_4$	0.5	85
Me_3C	$PhCH_2$	1	47–48[a]
2,4,6-$Me_3C_6H_2$	Et	0.5–4	0[b]
$CNCH_2$	$PhCH_2$	0.25	96
MeCHBr	$PhCH_2$	0.25	88
$MeCH_2CHBr$	Et	0.25	90
PhCH=CH(*trans*)	Et	0.5	90
$PhCO(CH_2)_2$	Et	0.25	94
$PhCONHCH_2$	Et	0.5	72
	Et	0.25	95
$HO(CH_2)_5$	Et	0.25	27
$HO(CH_2)_{10}$	Et	0.25	67

[a]The yield depends upon the molar equivalents of 4-(dimethylamino) pyridine used.
[b]Only the acid anhydride was isolated (81–98%) using these reagents.

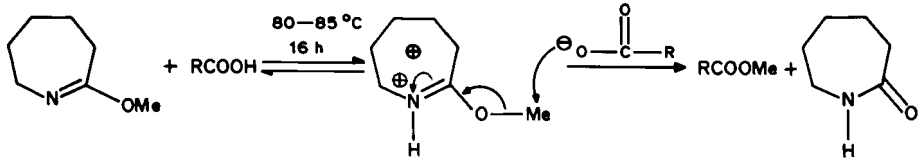
$$RCOOH + ClCOOCH_2CCl_3 + Et_3N \xrightarrow[CH_2Cl_2]{4\text{-Pyr}NMe_2} RCOOCH_2CCl_3 \qquad (944)$$

R	Method	Rx temp. (°C)	Rx time (h)	Yield (%)[a]
n-C_7H_{15}	—	0–25	1	50[b]
n-C_7H_{15}	A	0	0.3	50
n-C_7H_{15}	A	−78	0.5	90
n-C_7H_{15}	B	0	0.1–0.2	85–87[c]
n-C_7H_{15}	B	−78	0.2–0.5	75–90[c]
Ph	—	0–25	16	42
Ph	A	−78	0.3–0.7	5–20[c]
Ph	B	−78	0.2–0.3	30–35[c]
Ph	B	25	0.1	55–65[c]
Ph_2CH	—	25	0.2	80
Ph_2CH	A	−78	0.2	99
Ph_2CH	B	0	0.2	99

[a]Yields are reported as product ratios of the esters to the carbonate by-products.
[b]No 4-(dimethylamino)pyridine catalyst was used.
[c]The yield depends upon the molar ratio of 4-(dimethylamino)pyridine used.

The use of chloroformates to prepare esters of N-protected α-amino acids without loss of optical activity was also reported in the same reference[1972] with the results (equation 945) reported below.

An interesting preparation[1973] of the methyl esters of carboxylic acids involves the use of *O*-methylcaprolactim in place of an alcohol. Reaction of this reagent with carboxylic acids at 80–85 °C without the use of a solvent affords the corresponding methyl esters (equation 946) in 72–91% yields. The mechanism of the reaction involves the conversion of the *O*-methylcaprolactim to its conjugate acid in the presence of a carboxylic acid followed by attack of the conjugate acid on the carboxylate anion to produce the ester.

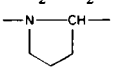
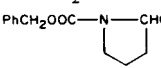


(946)

Acid	*Yield* (%)
PhCOOH	91
p-$AnCH_2COOH$	76
2-NaphCOOH	96
$HOOC(CH_2)_4COOH$	72
$Me_2C{=}CHCOOH$	78
o-HOC_6H_4COOH	80
p-$AnCH{=}CHCOOH$(*trans*)	73

Simple and substituted alkyl halides have been reported to be effective reagents for use in conjunction with carboxylic acids to produce esters. A variety of reagents and catalysts

$$\text{ProNH—CHRCOOH} + \text{ClCOOR}^1 \xrightarrow[0\,^\circ\text{C, 30 min}]{\text{4-Pyr NMe}_2,\ \text{CH}_2\text{Cl}_2} \text{ProNH—CHRCOOR}^1 \qquad (945)$$

Amine protecting group (Pro)	R	R^1	Product	Yield (%)
$PhCH_2OOC$	Me	Me	$PhCH_2OOCNHCH(Me)COOMe$	96
t-BuOOC	*i*-Pr	Me	*t*-BuOOCNHCH(*i*-Pr)COOMe	95
$PhCH_2OOC$	*i*-Pr	Et	$PhCH_2OOCNHCH(i\text{-Pr})COOEt$	94
$PhCH_2OOC$	$PhCH_2$	Et	$PhCH_2OOCNHCH(CH_2Ph)COOEt$	98
t-BuOOC	$PhCH_2$	$PhCH_2$	*t*-BuOOCNHCH(CH_2Ph)$COOCH_2Ph$	93
t-BuOOC	*i*-Pr	$PhCH_2$	*t*-BuOOCNHCH(*i*-Pr)$COOCH_2Ph$	91
$PhCH_2OOC$	Me_2CHCH_2	*p*-$O_2NC_6H_4$	$PhCH_2OOCNHCH(CH_2CHMe_2)COOC_6H_4NO_2$-*p*	98
t-BuOOC	CH_2COOCH_2Ph	Me	*t*-BuOOCNHCH(CH_2COOCH_2Ph)COOMe	88
$PhCH_2OOC$	$CH_2CH_2COOCH_2Ph$	Et	$PhCH_2OOCNHCH(CH_2CH_2COOCH_2Ph)COOEt$	96
$PhCH_2OOC$		*p*-$O_2NC_6H_4$		91

have been employed to effect esterification of carboxylic acids with these halides, and examples of these reactions are reported in this section.

One general method which allows the direct esterification of carboxylic acids with alkyl bromides to form esters involves the reaction[1974] of mercury(II)oxide/tetrafluoroboric acid in a chlorinated solvent (equation 947).

$$R^1COOH + R^2Br \xrightarrow[\text{2. } Na_2CO_3 \text{ 3. 1N aq. KOH}]{\text{1. HgO, HX, solvent, 20–80 °C; 1–3 h}} R^1COOR^2 \quad (947)$$

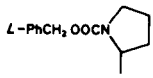
R^1	R^2	X in HX	Solvent	Temp. (°C)	Time (h)	Yield (%)
n-Bu	$PhCH_2$	BF_4	CH_2Cl_2	20	1	50
n-C_7H_{15}	*t*-Bu	F	$ClCH_2CH_2Cl$	80	1	58
Ph	Et	BF_4	CH_2Cl_2	20	2	53
Ph	*n*-Bu	BF_4	CH_2Cl_2	20	2	50
Ph	*n*-C_7H_{15}	BF_4	CH_2Cl_2	20	2	65
Ph	*n*-C_7H_{15}	F	$ClCH_2CH_2Cl$	80	1	52
Ph	*n*-C_8H_{17}	BF_4	CH_2Cl_2	20	2	64
Ph	*c*-C_6H_{11}	BF_4	CH_2Cl_2	20	1	55
Ph	*t*-Bu	BF_4	CH_2Cl_2	20	1	50
$PhCH_2$	Et(Me)CH	BF_4	CH_2Cl_2	20	3	38
$PhCH_2$	Et(Me)CH	F	$ClCH_2CH_2Cl$	80	1	35
$PhCH_2$	Et(Me)CH	*a*	CH_2Cl_2	20	1	57
$PhCH_2$	Et(Me)CH	*b*	CH_2Cl_2	20	3	30
$PhCH_2$	*c*-Hex	F	CH_2Cl_2	20	3	34
$PhCH_2$	$PhCH_2$	BF_4	$ClCH_2CH_2Cl$	80	1	60
$PhCH_2$	$PhCH_2$	F	$ClCH_2CH_2Cl$	80	1	79
$PhCH_2$	$PhCH_2$	No HX	CH_2Cl_2	20	1	71
Ph_2CH	Et	F	CH_2Cl_2	20	3	32
Ph_2CH	$H_2C{=}CHCH_2$	No HX	CH_2Cl_2	20	3	40

[a]Catalyst used was $Hg(BF_4)_2$. HgO in a 1:1 ratio.
[b]Catalyst used was $Hg(BF_4)_2$. HgO in a 1:4 ratio.

A similar preparation[1975] involves the reaction of carboxylic acids including simple aliphatic and aromatic acids, sterically hindered acids, thermally unstable acids and N-protected amino acids with alkyl halides in the presence of 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) in benzene (equation 948).

$$R^1COOH + R^2X \xrightarrow{DBU,\ C_6H_6} R^1COOR^2 + DBU\cdot HX \quad (948)$$

R^1	R^2X	Temp (°C)	Time (h)	Yield (%)
Me	$PhCH_2CH_2Br$	80	3	86
Me	$Me(CH_2)_5CHBrMe$	80	10	91
Me	*p*-$BrC_6H_4COCH_2Br$	80	1	89
Me_3C	*n*-C_4H_9Br	80	2	81
Me_3C	*s*-C_4H_9Br	80	3	86

R^1	R^2X	Temp (°C)	Time (h)	Yield (%)
Me_3C	$Me(CH_2)_5CHBrMe$	80	3	80
Me_3C	$PhCH_2CH_2Br$	80	3	90
$Me_2C{=}CH$	EtBr	80	2	80
$NCCH_2$	n-C_4H_9Br	80	2	91
$HOOCCH_2$	EtI	25	10	84[a]
2-Furyl	EtBr	80	3	90
Ph	EtI	25	1.5	95
Ph	$MeSCH_2Cl$	80	2	81
p-HOC_6H_4	EtBr	80	5	81
p-$H_2NC_6H_4$	EtBr	80	4	70
p-$Me_2NC_6H_4$	EtBr	80	3	85
2,4,6-$Me_3C_6H_2$	EtI	25	2	80
2,4,6-$Me_3C_6H_2$	p-$BrC_6H_4COCH_2Br$	80	2	70
2,4,6-$Me_3C_6H_2$	s-C_4H_9Br	80	6	91
L-$PhCH_2OOCNHCHMe$	MeI	80	2	92
	MeI	80	2	90.4
L-$PhCH_2OOCNHCHCHMe_2$	EtBt	80	1	94.6
L-$PhCH_2OOCNHCHCHMe_2$	EtBr	80	2	98.8
L-$PhCH_2OOCNHCHCHMe_2$	EtBr	80	3	99.2
L-$PhCH_2OOCNHCHCH_2Ph$	EtBr	80	2	99
L-$PhCH_2OOCNHCHCH_2CHMe_2$	EtBr	80	2	94.9
L-$PhCH_2OOCNHCHCH_2OH$	$PhCH_2Br$	80	2	92.9
L-$PhCH_2OOCNHCHCH(OH)Me$	$PhCH_2Br$	80	2	92.3
L-$PhCH_2OOCNHCHCH_2OH$	p-$O_2NC_6H_4CH_2Br$	80	2	95.7
L-$PhCH_2OOCNHCHCH(OH)Me$	p-$O_2NC_6H_4CH_2Br$	80	2	100
L-$Me_3COOCNHCHCH_2CONH_2$	$PhCH_2Br$	80	2	81.4
L-$Me_3COOCNHCH(CH_2)_2CONH_2$	$PhCH_2Br$	80	2	80.1

[a] Yield of diethyl ester.

Reaction of carboxylic acids with α-bromoacetophenone in the presence of potassium fluoride in *N*,*N*-dimethylformamide[1976] (equation 949) produces the corresponding phenacyl esters in excellent isolated yields ranging from 91–99%.

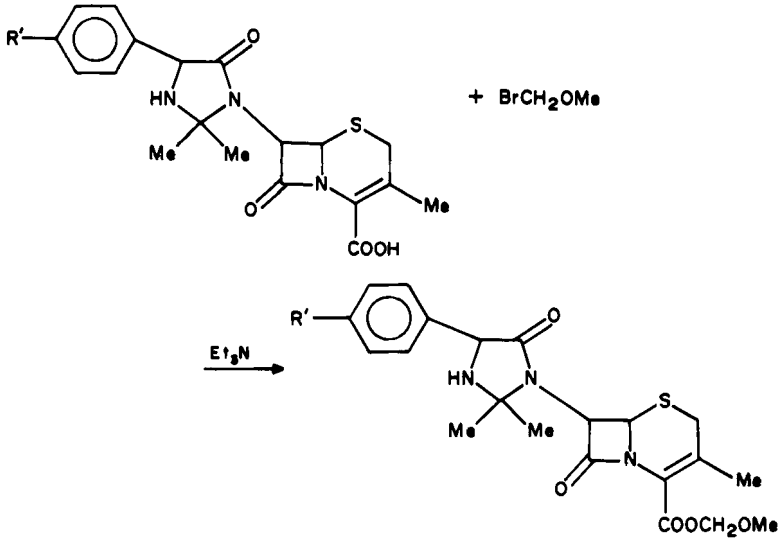
$$RCOOH + PhCOCH_2Br \xrightarrow[\text{temp., time}]{KF,\ DMF} RCOOCH_2COPh \qquad (949)$$

R	Temp. (°C)	Time (min)	Isolated yield (%)
Me	25	10	98
Me	118[a]	10	98
Et	25	10	95
Et	141[a]	10	93
t-Bu	25	10	95
t-Bu	100[a]	10	91
n-$C_{15}H_{31}$	100	10	96
Ph	25	10	98
o-An	25	3	99
p-$Me_3CC_6H_4$	25	60	99
p-$Me_3CC_6H_4$	100	10	97
2,4,6-$Me_3C_6H_2$	25	20	96

[a]No solvent was used.

Bromodimethyl ether in the presence of triethylamine has been reported[1977] to react with imidazolidinyl-3-methyl-3-cephem-4-carboxylic acids to produce (equation 950) the corresponding methoxymethyl esters, while reaction[1978] of dichloro- (equation 951) and chloro(phenyl)cyclobutanone (equation 952) with both simple and hindered carboxylic acids produces keto esters via a *cine* substitution.

Another interesting reaction[1979] which utilizes a halide for esterification involves treatment of iodoferrocene with a carboxylic acid in the presence of copper(I) oxide in refluxing acetonitrile (equation 953).



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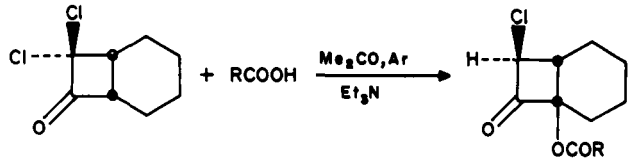
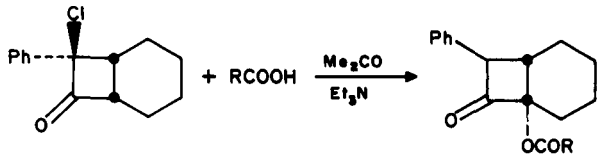


(951)

R=H, Me, $PhCH_2$, 2,4,6-$Me_3C_6H_2$, Me_3C



(952)

R =	Me	Ph	*o*-An, 2,4,6-$Me_3C_6H_2$	$PhCH_2$
% Yield =	82	81	82	–	60

$$\text{Iodoferrocene} + \text{RCOOH} \xrightarrow[\substack{\text{MeCN}\\ \text{reflux}}]{Cu_2O} \text{RCOO(ferrocenyl)} \equiv \text{acyloxyferrocene} \quad (953)$$

R	Yield (%)
Me	94
$ClCH_2$	49
$MeOCH_2$	83
$MeCONHCH_2$	67
Ph	92
o-ClC_6H_4	81
p-Tol	93
PhCH=CH	83

At least one report[1980] has appeared which demonstrates the use of primary amines in the esterification of carboxylic acids. Treatment of the primary amines with a small excess of a carboxylic acid and isoamyl nitrate in refluxing benzene causes aprotic deamination of the primary amine and resultant formation of the corresponding carboxylic ester with minimal rearrangement (equation 954).

$$RNH_2 + R^1COOH + Me_2CH(CH_2)_2ONO \xrightarrow[\text{reflux}]{C_6H_6} R^1COOR \quad (954)$$

R	R^1	Yield (%)
n-Bu	Ph	65
n-Bu	*p*-ClC_6H_4	62
n-Bu	*p*-An	64
i-Bu	Ph	46
s-Bu	Ph	30
t-Bu	Ph	2[a]
$PhCH_2CH_2$	Me	84
$PhCH_2CH_2$	CF_3	70
c-Hex	Me	50
$Me(CH_2)_{11}$	Me	66

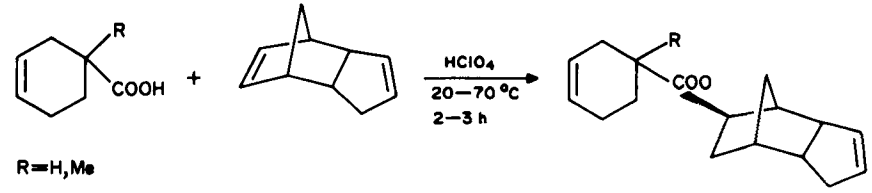
[a]Ester is unstable.

Molecules containing double and triple bonds, when used in conjunction with a wide variety of catalysts, are effective reagents in forming esters of carboxylic acids. Thus, liquid-phase esterification[1981] of acetic acid with ethylene using an acidic metal salt of tungsten produces ethyl acetate (equation 955), whereas reaction of propene with acetic acid in the presence of a small amount of potassium acetate, an aluminosilicate mixture as catalyst[1982] [made by reacting palladium chloride, silica, tetra-(*n*-propyl) ammonium bromide and sodium hydroxide] and oxygen at 180 °C produces a 97.8% yield of allyl acetate (equation 956).

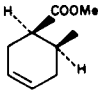
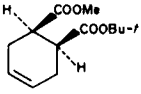
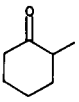
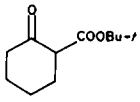
$$MeCOOH + CH_2{=}CH_2 \xrightarrow[H_2O,\ 210\,^\circ C,\ 3\,h]{H_4(SiW_{12}O_{40})} MeCOOEt \quad 38.6\% \tag{955}$$

$$MeCH{=}CH_2 + MeCOOH + MeCO\overset{\ominus}{O}K^{\oplus} \xrightarrow[(n\text{-}Pr)_4\overset{\oplus}{N}Br^{\ominus},\ silica,\ Al_2O_3,\ 182\,^\circ C]{PdCl_2,\ NaOH,} MeCOOCH_2CH{=}CH_2 \quad 97.8\% \tag{956}$$

Several more direct procedures using olefins in the preparation of esters have also been reported, including the preparation of dihydrodicyclopentadienyl cyclohexanoates by the reaction[1983] of the corresponding carboxylic acid with dicyclopentadiene in the presence of perchloric acid as a catalyst (equation 957), and the preparation[1984] of *t*-butyl esters by



$$RCOOH + MeCOOBu\text{-}t + t\text{-}BuOH \xrightarrow[0\ ^\circ C\ to\ r.t.]{H_2SO_4} RCOOBu\text{-}t \tag{958}$$

R	Product	Yield (%)
Ph	PhCOOBu-*t*	92
o-ClC_6H_4	*o*-ClC_6H_4COOBu-*t*	78
PhCH=CH	PhCH=CHCOOBu-*t*	62
p-$HOC_6H_4CH_2CH(NH_2)$	*p*-$HOC_6H_5CH_2CH(NH_2)COOBu$-*t*	82
$Ph(CH_2)_3$	$Ph(CH_2)_3COOBu$-*t*	75
$MeCOCH_2CH_2$	$MeCOCH_2CH_2COOBu$-*t*	66
MeCHBr	MeCHBrCOOBu-*t*	92
		87
		53
$BrCH_2CH_2$	$BrCH_2CH_2COOBu$-*t*	80

$$R^1C{\equiv}CR^2 + R^3COOH \xrightarrow[\substack{80\,^\circ C,\ \text{stir } 0.5\,h \\ 2.\ 110\,^\circ C,\ \text{stir } 6\,h}]{1.\ Ag_2CO_3,\ HOAc,\ N_2} R^3COOCR^1{=}CHR^2 \qquad (960)$$

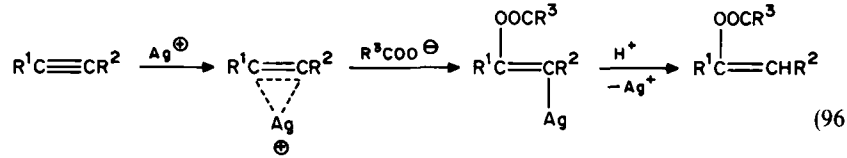
R^1	R^2	R^3	Product	Stereoisomeric Ratio[a]	Yield (%)
$MeCOOCH_2$	$MeCOOCH_2$	Me	$MeCOOCH_2C{=}CHCH_2COOMe$ OOCMe	8/2	80
$MeCOOCH_2$	$MeCOOCH_2$	Et	$MeCOOCH_2C{=}CHCH_2COOMe$ OOCEt	8/2	83
$MeCOOCH_2$	$MeCOOCH_2$	*n*-Pr	$MeCOOCH_2C{=}CHCH_2COOMe$ OOCPr-*n*	7/3	94
$MeCOOCH_2$	$MeCOOCH_2$	Ph	$MeCOOCH_2C{=}CHCH_2COOMe$ OOCPh	6/4	53
$MeOCH_2$	$MeOCH_2$	Me	$MeOCH_2C{=}CHCH_2OMe$ OOCMe	9/1	49
$MeOCH_2$	$MeOCH_2$	Et	$MeOCH_2C{=}CHCH_2OMe$ OOCEt	9/1	55
$MeOCH_2$	$MeOCH_2$	Ph	$MeOCH_2C{=}CHCH_2OMe$ OOCPh	9/1	69
MeOOC	MeOOC	Me	$MeOOCC{=}CHCOOMe$ OOCMe	9/1	60
H	$HOCH_2$	Me	$MeCOOCH{=}CHCH_2OOCMe$ + $CH_2{=}CCH_2OOCMe$ OOCMe (ratio 2:1)	— 6/4	63
Ph	$HOCH_2$	Me	$MeCOOCPh{=}CHCH_2OOCMe$	9/1	54
Ph	H	Me	$MeCOOCPh{=}CH_2$	—	28
Ph	Et	Me	$MeCOOCPh{=}CHEt$	—	0

[a] Definite stereochemical assignment of either (*E*)- or (*Z*)-isomers was not made.

the application of a modified Taschner's procedure, in which carboxylic acids are treated in a mixture of *t*-butyl acetate and *t*-butyl alcohol with sulfuric acid (equation 958). The mechanism for this reaction[1984] involves the intermediate formation of 2-methylpropene which then reacts with the carboxylic acid (equation 959) to form the ester.

$$MeCOOCMe_3 \xrightarrow{H_2SO_4} [MeCOOH + CH_2{=}CMe_2] \xrightarrow{RCOOH} RCOOCMe_3 \quad (959)$$

At least one procedure has been reported[1985] which involves the use of molecules containing triple bonds as reagents in the preparation of esters. Thus, reaction of acetylenic compounds with carboxylic acids in the presence of a silver salt catalyst produces enol esters (equation 960) in good yield. Of the catalysts used it was found that silver carbonate afforded the best yields. Although complicated, the mechanism for this reaction proposed by the authors[1985] involves initial electrophilic addition of the silver cation to the triple bond to form a π-complex, which then undergoes electrophilic attack by a carboxylate anion, followed by protonation to afford the enol ester (equation 961).



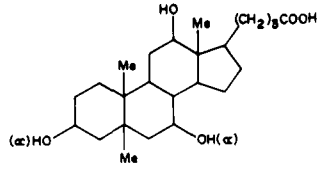
(961)

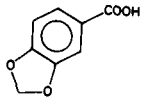
An example of one of the more traditional methods of methyl ester preparation is the reaction[1986] of 4-(ethylthio)-2,2-diphenylbutyric acid with diazomethane (equation 962). Although this method affords excellent yields of the methyl esters, it has always suffered in the extent of its use because of the explosive and highly toxic nature of the diazomethane reagent required. Recently, trimethylsilyldiazomethane, a stable and safe substitute for diazomethane, has been reported[1987] to produce methyl esters from carboxylic acids within 30 minutes at room temperature and in excellent yields (equation 963).

$$EtSCH_2CH_2C(Ph)_2COOH + CH_2N_2 \xrightarrow{ether} EtSCH_2CH_2C(Ph)_2COOMe \quad (962)$$

98%

$$RCOOH + Me_3SiCHN_2 \xrightarrow[\substack{\text{r.t. stir}\\ 30\,\text{min}}]{MeOH,\ C_6H_6} RCOOMe \quad (963)$$

Acid	Methyl ester yield (%)
n-$C_{15}H_{31}COOH$	100
c-HexCOOH	100
Thiophene-2-carboxylic acid	100
	100
$PhCH_2CH(NH_2)COOH$	42[a]
$Me(CH_2)_7CH{=}CH(CH_2)_7COOH$(*cis*)	100

Acid	Methyl ester yield (%)
$HOOC(CH_2)_2COCOOH$	85[b]
	100
o-HOC_6H_4COOH	100
o-$O_2NC_6H_4COOH$	95
o-$O_2NC_6H_4COOH$	87[c]
2,4,6-$Me_3C_6H_2COOH$	97
Pyridine-2-carboxylic acid	82

[a] Reaction time 4 hours; product was isolated as HCl salt.
[b] Ester obtained is $HOOC(CH_2)_2COCOOMe$.
[c] Reaction was run using EtOH in place of MeOH as solvent.

A significant number of reports have appeared describing the synthesis of alkylsilyl, thiol and selenol esters from carboxylic acids using a variety of reagents. Dimethylaminotrimethylsilane[1988] has been used to produce the trimethylsilyl esters of ω-(dimethylamino)alkanoic acids (equation 964) from ω-bromoalkanoic acids. This reaction is interesting because both the dimethylamino and the trimethylsilyl portion of the reagent are incorporated into the ester products. The authors report that the yield of the esters produced increases with increasing values of n.

$$Br(CH_2)_nCOOH + Me_2NSiMe_3 \xrightarrow{MeOH} Me_2N(CH_2)_nCOOSiMe_3 \qquad (964)$$

$n = 1\text{–}5$ 30–94%

Allyltrimethylsilane has also been reported[1989] to react as a silylating agent for carboxylic acids producing the corresponding trimethylsilyl esters (equation 965).

$$RCOOH + (CH_2{=}CHCH_2)SiMe_3 \xrightarrow[MeCN,\ 70\text{–}80\,^\circ C,\ stir]{p\text{-}MeC_6H_4SO_3H} MeCH{=}CH_2 + RCOOSiMe_3$$

R =	n-C_5H_{11}	Ph
Time(h) =	2.5	2.0
% Yield =	88	87

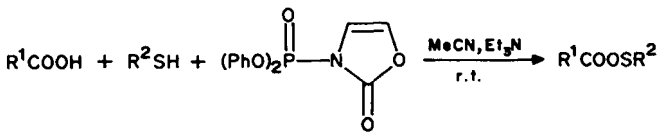
(965)

Reaction of trimethylsilylated N,N-dimethylcarbamate with carboxylic acids at room temperature for 10 minutes also is reported[1990] to produce the corresponding trimethylsilyl esters (equation 966).

$$RCOOH + Me_2NCOOSiMe_3 \xrightarrow[10\,min]{r.t.} RCOOSiMe_3 \qquad (966)$$

R =	Me	Ph
% Yield =	87	78

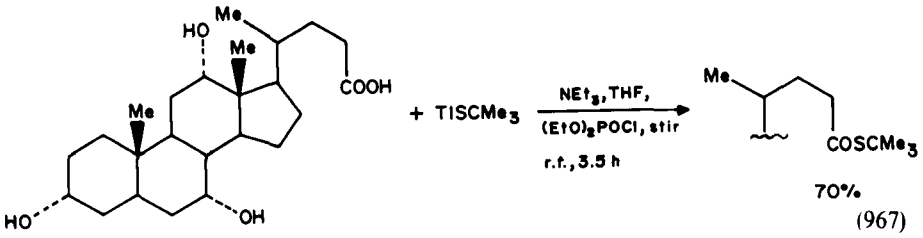
Several examples of the use of phosphorous-containing compounds, both as reagents and as coupling agents, in the preparation of thiol esters have been described. Thus, reaction of thallium(I) 2-methylpropane-2-thiolate with cholic acid produces[1991] the (t-butyl) thiol ester of cholic acid in 70% yield (equation 967) if the reaction is performed in the presence of diethyl phosphorochloridate and triethylamine.



(968)

Acid	Thiol	Rx time (h)	Product	Yield (%)
MeCOOH	$PhCH_2SH$	3	$MeCOOSCH_2Ph$	96
MeCOOH	PhSH	1	MeCOSPh	91
$Me(CH_2)_5CH(OH)(CH_2)_{10}COOH$	PhSH	1	$Me(CH_2)_5CH(OH)(CH_2)_{10}COSPh$	93
Me_3CCOOH	$PhCH_2SH$	2	$Me_3CCOSCH_2Ph$	87
$Me_3COOCNHCHCOOH$ CH_2CHMe_2	EtSH	4[a]	$Me_3COOCNHCHCOSEt$ CH_2CHMe_2	86
PhCOOH	PhSH	1	PhCOSPh	94
PhCOOH	*n*-BuSH	1	PhCOSBu-*n*	91
PhCOOH	*t*-BuSH	20	PhCOSBu-*t*	83
$Ph_2CHCOOH$	*n*-BuSH	2	$Ph_2CHCOSBu$-*n*	89
$Ph_2CHCOOH$	*t*-BuSH	20	$Ph_2CHCOSBu$-*t*	68

[a]At 0 °C.

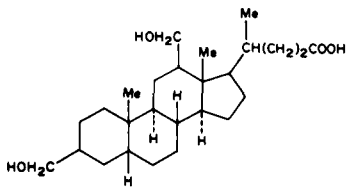
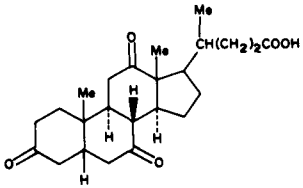
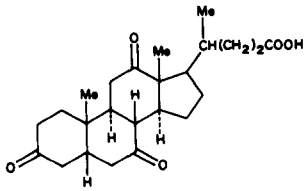


(967)

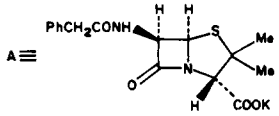
Another phosphorus-containing compound which has been found to be effective as a coupling agent in the preparation[1992] of thiol esters from carboxylic acids and thiols is diphenyl 2-oxo-3-oxazolinylphosphophosphonate (equation 968).

By reaction[1993] of carboxylic acids with *N,N*-dimethylphosphoramidic dichloride and triethylamine in dimethoxyethane followed by treatment with a thiol, a variety of thiol esters are produced in good yields (equation 969).

$$R^1COOH + Me_2NP(O)Cl_2 + Et_3N \xrightarrow[\text{stir 1 h}]{\text{1. DME, } N_2\text{, r.t.}} \xrightarrow[\text{2. } R^2SH\text{, stir 18 h}]{} R^1C(O)SR^2 \qquad (969)$$

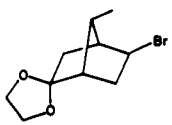
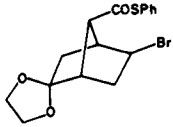
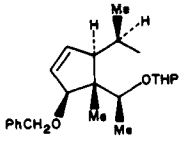
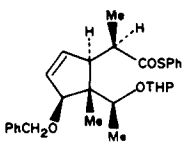
R^1COOH	Base	R^2SH	Yield (%)
PhOCH(Me)COOH	Et_3N	PhSH	97
PhOCH(Me)COOH	Et_3N	EtSH	100
PhOCH(Me)COOH	Et_3N	*i*-PrSH	93
PhOCH(Me)COOH	Et_3N	*t*-BuSH	71
PhCOOH	Et_3N	*i*-PrSH	74
PhCOOH	K_2CO_3	*t*-BuSH	68
c-$C_6H_{11}COOH$	C_5H_5N	PhSH	90
$CH_2{=}CH(CH_2)_8COOH$	C_5H_5N	*c*-$C_6H_{11}SH$	71
	Et_3N	PhSH	44
	Et_3N	EtSH	72
	Et_3N	PhSH	77

R^1COOH	Base	R^2SH	Yield (%)
A[a]	Et_3N	EtSH	81
A[a]	Et_3N	PhSH	82
A[a]	Et_3N	*n*-BuSH	82
A[a]	Et_3N	$PhCH_2SH$	74
A[a]	C_5H_5N	*i*-PrSH	79
A[a]	Et_3N	PhSH	86

[a] A ≡ 

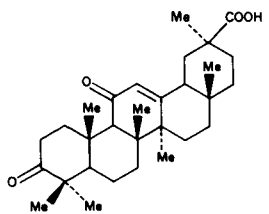
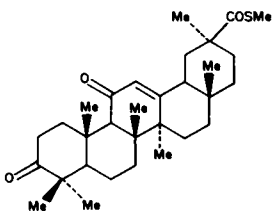
Reaction of carboxylic acids with phenylthiocyanates in the presence of tri-*n*-butylphosphine as a coupling agent produces[1994] benzenethiol esters according to equation 970.

$$RCOOH + PhSCN \xrightarrow[CH_2Cl_2,\ r.t.\ 30\,min]{(n\text{-}Bu)_3P,\ N_2} RCOSPh \qquad (970)$$

R	Product	Yield (%)
Me	MeCOSPh	92
$Me(CH_2)_6$	$Me(CH_2)_6COSPh$	81
$BrCH_2(CH_2)_5$	$BrCH_2(CH_2)_5COSPh$	80
Ph	PhCOSPh	96
$PhCH_2$	$PhCH_2COSPh$	94
p-An	*p*-AnCOSPh	96
p-ClC_6H_4	*p*-ClC_6H_4COSPh	92
c-Hex	*c*-HexCOSPh	91
c-Hex	*c*-$HexCOSC_6H_4NO_2$-*o*	86[a]
c-$HexCH_2$	*c*-$HexCH_2COSPh$	96
c-$HexCH_2$	*c*-$HexCH_2COSPyr$-2	0[b]
4-Cyclohexenyl	4-CyclohexenylCOSPh	92
		86[c]
		43[c]

[a] *o*-$O_2NC_6H_4SCN$ used as reagent in THF, at 25 °C for 4 hours.
[b] 2-Pyridinethiocyanate used as reagent.
[c] Reaction time was 3 hours.

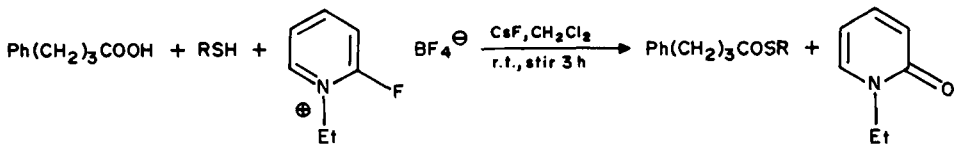
TABLE 89. Preparation of methylthiol esters using phosphonium salts[1995]

Acid	Base	Salt		Product	Yield (%)
PhCOOH	Me_2NPyr-4	$(n\text{-}Bu)_3\overset{\oplus}{P}SMe$	$\overset{\ominus}{O}SO_2C_6H_4Me$-*p*	PhCOSMe	63
PhCOOH	$(i\text{-}Pr)_2NEt$	$(n\text{-}Bu)_3\overset{\oplus}{P}SMe$	$\overset{\ominus}{O}SO_2C_6H_4Me$-*p*	PhCOSMe	69
PhCOOH	$(i\text{-}Pr)_2NEt$	$(n\text{-}Bu)_3\overset{\oplus}{P}SMe$	$\overset{\ominus}{O}SO_2CF_3$	PhCOSMe	67
PhCOOH	$(i\text{-}Pr)_2NEt$	$Me_3\overset{\oplus}{P}SMe$	$\overset{\ominus}{O}SO_2CF_3$	PhCOSMe	72
$Me(CH_2)_6COOH$	Me_2NPyr-4	$(n\text{-}Bu)_3\overset{\oplus}{P}SMe$	$\overset{\ominus}{O}SO_2C_6H_4Me$-*p*	$Me(CH_2)_6COSMe$	70
$Me(CH_2)_6COOH$	Me_2NPyr-4	$Me_3\overset{\oplus}{P}SMe$	$\overset{\ominus}{O}SO_2CF_3$	$Me(CH_2)_6COSMe$	80
$(E)Me(CH_2)_4CH{=}CHCOOH$	Me_2NPyr-4	$(n\text{-}Bu)_3\overset{\oplus}{P}SMe$	$\overset{\ominus}{O}SO_2C_6H_4Me$-*p*	$(E)Me(CH_2)_4CH{=}CHCOSMe$	58
$(E)Me(CH_2)_4CH{=}CHCOOH$	$(i\text{-}Pr)_2NEt$	$(n\text{-}Bu)_3\overset{\oplus}{P}SMe$	$\overset{\ominus}{O}SO_2C_6H_4Me$-*p*	$(E)Me(CH_2)_4CH{=}CHCOSMe$	55
	Me_2NPyr-4	$(n\text{-}Bu)_3\overset{\oplus}{P}SMe$	$\overset{\ominus}{O}SO_2CF_3$		70

One example[1995] of a phosphorus-containing class of compounds used as a reagent in the preparation of methylthiol esters from carboxylic acids is the methylthiophosphonium salts. The following examples of this class of compounds have been used successfully to produce methylthiol esters: (1) methylthiotri(*n*-butyl)phosphonium trifluoromethanesulfonate, prepared by reaction of tri-(*n*-butyl)phosphine sulfide with trifluoromethanesulfonate in benzene at room temperature; (2) methylthiotri(*n*-butyl)phosphonium *p*-toluenesulfonate, prepared by reaction of tri-(*n*-butyl)phosphine sulfide with methyl *p*-toluenesulfonate in refluxing carbon tetrachloride or benzene; and (3) methylthiotrimethylphosphonium trifluoromethanesulfonate, prepared by reaction of trimethylphosphine sulfide with methyl trifluoromethanesulfonate in toluene at room temperature. The general reaction for this method of preparation of thiol esters is shown in equation 971, with more specific information given in the entries listed in Table 89.

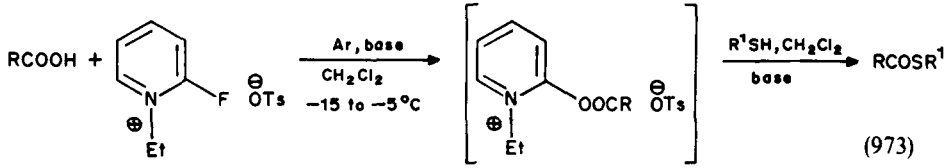
$$\text{RCOOH} + \text{methylthiophosphonium salt} \xrightarrow[\substack{1.\ C_6H_6,\ 60\,^\circ C \\ 2.\ \text{stir, r.t., 24 h}}]{\text{base}} \text{RCOSR}^1 \qquad (971)$$

Thiol esters have also been prepared from carboxylic acids by the use of nitrogen containing compounds as both coupling agents and reactants. By using 2-fluoro-1-ethylpyridinium tetrafluoroborate[1996] in the presence of cesium fluoride (equation 972) or 2-fluoro-1-methylpyridinium *p*-toluenesulfonate[1997] in presence of an amine base (equation 973) as coupling agents, carboxylic acids and thiols can be effectively condensed to produce thiol esters.



R= Ph PhCHMe
yield (%)= 93 93

(972)



(973)

base = Et_3N or $(n\text{-}Bu)_3N$

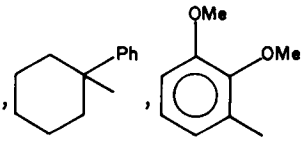
R in acid	R^1 in thiol	Conditions: Step 1 Temp. (°C)	Step 1 Time (min)	Step 2 Temp. (°C)	Step 2 Time (min)	Yield (%)
Ph	Ph	−15 to −5	60	−15 to −5	120	87
$PhCH_2$	Ph	−15 to −5	60	−15 to −5	120	96
$PhCH_2$	Ph	−15 to −5	60	−15 to −5	120	84[a]
Me_3C	Ph	−15 to −5	60	−15 to −5	120	88
$MeCO(CH_2)_2$	Ph	−15 to −5	60	−15 to −5	120	83

R in acid	R^1 in thiol	Conditions: Step 1 Temp. (°C)	Step 1 Time (min)	Step 2 Temp. (°C)	Step 2 Time (min)	Yield (%)
$HOOC(CH_2)_4$	Ph	−15 to −5	60	−15 to −5	120	79[b]
$PhCH_2$	*n*-Bu	−15 to −5	60	−15 to −5	120	81[a]
$PhCH_2$	*s*-Bu	−15 to −5	60	Reflux	120	81
$PhCH_2$	*t*-Bu	−15 to −5	20	r.t.	Overnight	84
$PhCH_2$	α-C_5H_5N	−15 to −5	30	r.t.	Overnight	79
 —CMe_2—	Ph	−15 to −5	15	−15 to −5	35	84
$Me(CH_2)_5CH(OH)$—$(CH_2)_{10}$	Ph	r.t.	30	r.t.	60	75

[a]Tri(*n*-butyl)amine used as the base.
[b]Product obtained was $PhSOC(CH_2)_4COSPh$.

The use of *p*-dimethylaminopyridine in conjunction with dicyclohexylcarbodiimide[1998] (equation 974) or 2,4,6-trinitrofluorobenzene[1999] (equation 975) has been reported to catalyze the reaction of carboxylic acids and thiols to produce thiol esters.

$$RCOOH + R^1SH \xrightarrow[DCCD]{Me_2NPyr\text{-}4} RCOSR^1 \qquad (974)$$

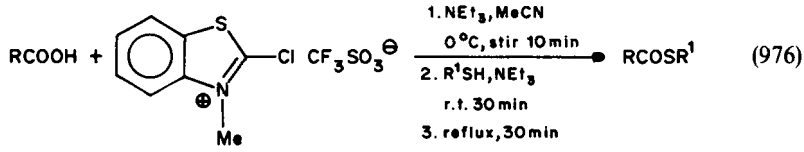
R = *c*-C_6H_{11}, (*E*)-PhCH=CH, Me_3C, 

$R^1 = Me_2NCH_2CH_2$ 2-An 2-Pyr

$$RCOOH + R^1SH + \text{Picryl fluoride} \xrightarrow[\substack{MeCN,\ r.t.\\ stir\ 4\ h}]{Me_2N\,Pyr\text{-}4} RCOSR^1 \qquad (975)$$

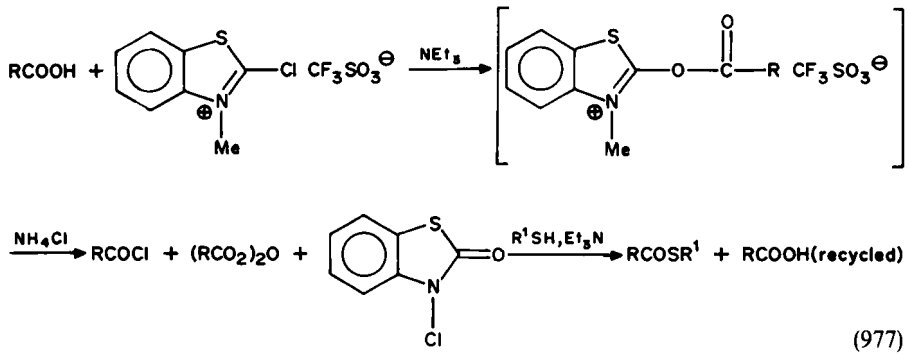
Acid	Thiol	Rx time (h)	Product	Yield (%)
PhCOOH	*n*-BuSH	4	PhCOSBu-*n*	95
PhCOOH	*t*-BuSH	15	PhCOSBu-*t*	95
PhCOOH	PhSH	3	PhCOSPh	98
PhCH=CHCOOH (*trans*)	*n*-BuSH	1	PhCH=CHCOSBu-*n* (*trans*)	92
PhCH=CHCOOH (*trans*)	*s*-BuSH	12	PhCH=CHCOSBu-*s* (*trans*)	87
PhCH=CHCOOH (*trans*)	*t*-BuSH	24	PhCH=CHCOSBu-*t* (*trans*)	94
PhCH=CHCOOH (*trans*)	PhSH	12	PhCH=CHCOSPh (*trans*)	97
n-$C_{17}H_{35}COOH$	*n*-BuSH	12	*n*-$C_{17}H_{35}COSBu$-*n*	84
n-$C_{17}H_{35}COOH$	*s*-BuSH	24	*n*-$C_{17}H_{35}COSBu$-*s*	80
$Ph_2CHCOOH$	*n*-BuSH	24	$Ph_2CHCOSBu$-*n*	36
$Ph_2CHCOOH$	PhSH	24	$Ph_2CHCOSPh$	46
Me_3CCOOH	*n*-BuSH	24	$Me_3CCOSBu$-*n*	44

Reaction of commercially available 2-chlorobenzothiazole and methyl trifluoromethanesulfonate produces 2-chloro-*N*-methylbenzothiazolium trifluoromethanesulfonate which is reported[2000] to be an efficient condensing agent for the preparation of thiol esters in good yields using mild, nonacidic conditions from carboxylic acids and thiols (equation 976). The mechanism proposed[2000] for this reaction involves exothermic condensation of the carboxylic acid with the 2-chloro-N-methylbenzothiazolium trifluoromethanesulfonate in the presence of triethylamine to form *N*-methylbenzothiazolidone and the acid chloride (equation 977), a part of which is converted into the corresponding acid anhydride (author estimate = 10–30%). Since the reaction of the acid anhydride with the thiol proceeds more slowly that the reaction of the acid chloride with the thiol, refluxing the reaction is recommended for completion. The carboxylic acid produced appears to be recycled, at least in part, to raise the overall yield of thiol ester produced.



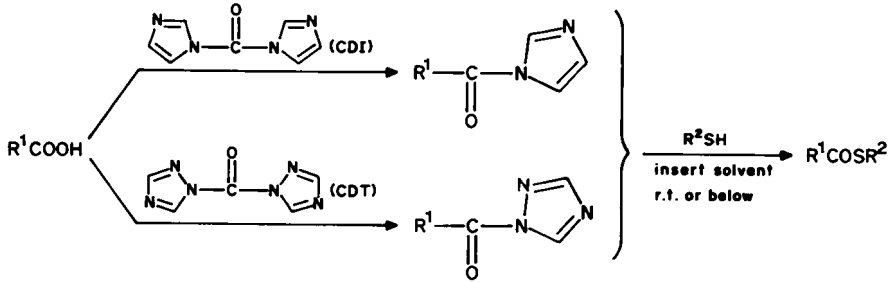
(976)

Acid	Thiol	Product	Yield (%)
c-HexCOOH	*n*-HexSH	*c*-HexCOSHex-*n*	85
c-HexCOOH	PhSH	*c*-HexCOSPh	91
PhCOOH	*n*-HexSH	PhCOSHex-*n*	75
PhCOOH	PhSH	PhCOSPh	80
n-C_7H_{15}COOH	*n*-HexSH	*n*-C_7H_{15}COSHex-*n*	92
n-C_7H_{15}COOH	PhSH	*n*-C_7H_{15}COSPh	90

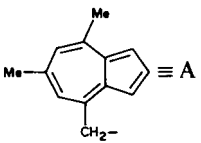


(977)

Another preparation[2001] of thiol esters involves the reaction of carboxylic acids in inert, anhydrous solvents, such as DMF or ethyl acetate, at or below room temperature with carbonyldiimidazole (CDI) or carbonyldi-1,2,4-triazole (CDT) to give almost quantitative yields of 1-acylimidazoles or 2-acyl-2*H*-1,2,4-triazoles. These unisolated intermediates are then allowed to react with added thiols to produce 71–97% of the corresponding thiol esters (equation 978).



(978)

R^1	R^2	Yield (%)[a]	R^1	R^2	Yield (%)[a]
Ph	Ph	97	$Me(CH_2)_{16}$	Ph	94
Ph	Et	89	$Me(CH_2)_{16}$	Et	86
Ph	Me_2CH	95	$Me(CH_2)_{16}$	Me_2CH	92
Ph	*t*-Bu	92	$Me(CH_2)_{16}$	*t*-Bu	88
Ph	CH_2COOH	91	 ≡ A	Ph	91
Ph	$(CH_2)_2COOH$	84			
Ph	2-Pyr	86[b]	A	Et	86
Ph	$(CH_2)_2OH$	89	A	Me_2CH	89
t-Bu	Ph	92			
t-Bu	Et	93	$Me(CH_2)_7CH=CH(CH_2)_7$ (*trans*)	Ph	91
t-Bu	Me_2CH	86			

(*continued*)

R^1	R^2	Yield (%)[a]	R^1	R^2	Yield (%)[a]
t-Bu	Me_3C	86	$Me(CH_2)_7CH{=}CH(CH_2)_7$— (*trans*)	Et	86
c-Hex	Ph	94			
c-Hex	Et	90	$Me(CH_2)_7CH{=}CH(CH_2)_7$— (*trans*)	Me_2CH	91
c-Hex	Me_2CH	92			
c-Hex	Me_3C	93	$Me(CH_2)_7CH{=}CH(CH_2)_7$— (*trans*)	*t*-Bu	84
$(CH_2)_4(COOH)_2$[g]	Ph	83			
$(CH_2)_4(COOH)_2$[g]	Et	87	MeSCH=C(SMe) (*cis*)	*c*	87
$(CH_2)_4(COOH)_2$[g]	Me_2CH	81			
$PhCH_2OOCNHCHCH_2Ph$	Ph	89	MeSCH=C(SMe) (*cis*)	*d*	71[e]
$PhCH_2OOCNHCHCH_2Ph$	Et	91	*f*	Ph	83
$PhCH_2OOCNHCHCH_2Ph$ D	Me_2CH		*f*	Et	81
			f	Me_2CH	84

[a] Imidazolide method used unless otherwise specified.
[b] Triazolide method used.
[c] 1,5-dioxo-9-thiaspiro-{5.5}-undec-8-yl.
[d] 4-hydroxy-1-thiacyclohex-2-yl.
[e] Mixture of two diastereoisomers in the ratio 1:1.
[f] 11-hydroxy-*trans*-8-heptadecyl (ricinelaidic acid).
[g] The product is $R^2SC(O)(CH_2)_4C(O)SR^2$.

Another class of esters formed by direct esterification of carboxylic acids is selenol esters, which have been prepared by three of the methods already discussed for the preparation of thiol esters. Thus if sulfur were replaced by selenium in the reactions shown in equations 970, 971 and 978, then the new equations would be a proper representation of the methods used to prepare the selenol esters. Table 90 lists the selenol esters prepared by any of the three methods listed above.

A report[2002] has recently appeared describing the preparation of silyl esters of carbamic acids. By reaction of amines, trimethylsilyl substituted amines or trimethylsilyl substituted hydrazines with carbon dioxide several examples of trimethylsilyl esters of carbamic acids have been prepared (equation 979).

$$RR^1NH + CO_2 \longrightarrow [RR^1NCOOH] \xrightarrow{HN(SiMe_3)_2} RR^1NCOOSiMe_3 \quad (979)$$

40–99%

R = H
R^1 = Me, alkyl, *n*-Bu, Ph
or $R—R^1 = (CH_2)_5$

$R^1{}_2NNR^2SiMe_3$
R^1 = Me, Et
R^2 = H, Pr
or $R^1 = MeC_6H_4$ and R^2 = H
$Me_2Si(OR^1)CH_2NR^2SiMe_3$

R^1 = H, Me
R^2 = alkyl, H, Me_2CHCH_2, *n*-Bu

CO_2

→ $R^1{}_2NNR^2COOSiMe_3$ 69–91%

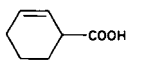
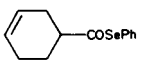
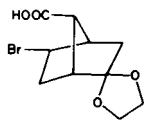
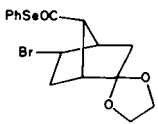
→ $Me_2Si(OR^1)CH_2NR^2COOSiMe_3$

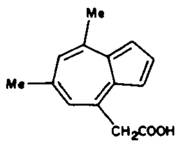
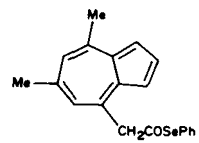
*2. *Alkylation of carboxylate salts*

Preparation of esters by alkylation of carboxylate salts can be accomplished using a variety of alkylating agents, carboxylate salts, coupling agents and reaction conditions. Alkyl halides are by far the most common alkylating agents for effecting ester preparation from carboxylate salts, regardless of the salts used which range from potassium, sodium and tetraalkylammonium to triarylsulfonium. The material in this section is organized by the type of carboxylate salt alkylated, beginning with potassium salts.

In addition to the direct condensation of a potassium carboxylate salt with a halide in the presence of a simple solvent to produce the corresponding ester, as illustrated by the reaction of potassium propionate with 17β-(bromoacetoxy)-16 β-ethylestran-4-en-3-one (equation 980) to produce[2003] the corresponding double ester, potassium carboxylates have also been treated with alkyl halides in the presence of nitrogen-containing solvents and condensing agents. Catalytic activation[2004] of potassium carboxylates using TMEDA in a two-phase solid–liquid media permits condensation of the salt with both simple and sterically hindered halides to produce the corresponding (equation 981) simple and sterically hindered carboxylic acid esters (Table 91). Ammonium salts have also been used[2005] as a solid–liquid phase-transfer catalyst without added solvent to catalyze the condensation of potassium carboxylates and alkylating agents (equation 982). Two methods have been used to effect this condensation. In Method A, the potassium salt is first prepared by reaction of the carboxylic acid with potassium hydroxide, isolated and then allowed to react with the alkylating agent in the presence of the ammonium salt catalyst, with shaking, for 15 minutes. Using Method B, a mixture of the carboxylic acid, finely ground potassium hydroxide, and the ammonium salt is shaken at room temperature for

TABLE 90. Selenol esters by various methods

Carboxylic Acid	Reagent	Reaction conditions	Equation	Product	Yield (%)	Reference
MeCOOH	PhSeCN	2.5 h, THF	970	MeCOSePh	79	1994
$Me(CH_2)_6COOH$	PhSeCN	3.0 h	971	$Me(CH_2)_6COSePh$	78	1994
$Me(CH_2)_{16}COOH$	PhSeH	CDT[a]	978	$Me(CH_2)_{16}COSePh$	94	2001
Me_3CCOOH	PhSeH	CDT[a]	978	$Me_3CCOSePh$	90	2001
c-HexCOOH	PhSeH	CDT[a]	978	*c*-HexCOSePh	94	2001
c-HexCOOH	PhSeCN	2.0 h	970	*c*-HexCOSePh	88	1994
c-HexCOOH	*o*-$O_2NC_6H_4SeCN$	*b*	970	*c*-$HexCOSeC_6H_4NO_2$-*o*	30	1994
c-$HexCH_2COOH$	PhSeCN	3.0 h	970	*c*-$HexCH_2COSePh$	78	1994
	PhSeCN	3.5 h	970		84	1994
$Me(CH_2)_4CH{=}CHCOOH$ (*trans*)	$(n\text{-}Bu)_3\overset{+}{P}SeMe$ OSO_2CF_3	$(i\text{-}Pr)_2NEt$	971	$Me(CH_2)_4CH{=}CHCOSeMe$ (*trans*)	50	1995
$Me(CH_2)_7CH{=}CH(CH_2)_7COOH$ (*trans*)	PhSeH	CDT[a]	978	$Me(CH_2)_7CH{=}CH(CH_2)_7COSePh$ (*trans*)	88	2001
	PhSeCN	3.0 h	970		46	1994

PhCOOH	$(n\text{-Bu})_3\overset{+}{P}SeMe$ $\bar{O}SO_2C_6H_4Me\text{-}p$	$Me_2NPyr\text{-}4$	971	PhCOSeMe	70	1995
PhCOOH	$(n\text{-Bu})_3\overset{+}{P}SeMe$ $\bar{O}SO_2CF_3$	$Me_2NPyr\text{-}4$	971	PhCOSeMe	64	1995
PhCOOH	PhSeCN	2.0 h	970	PhCOSePh	84	1994
PhCOOH	PhSeH	CDT	978	PhCOSePh	92	2001
p-AnCOOH	PhSeCN	0.5 h	970	*p*-AnCOSePh	83	1994
p-ClC_6H_4COOH	PhSeCN	0.3 h	970	*p*-$ClC_6H_4COSePh$	36	1994
$PhCH_2OOCNHCH(CH_2Ph)COOH$	PhSeH	CDT	978	$PhCH_2OOCNHCH(CH_2Ph)COSePh$	89	2001
	PhSeH	CDT[a]	978		94	2001

[a]CDT = carbonylide-1,2,4-trizole.
[b]Not reported.

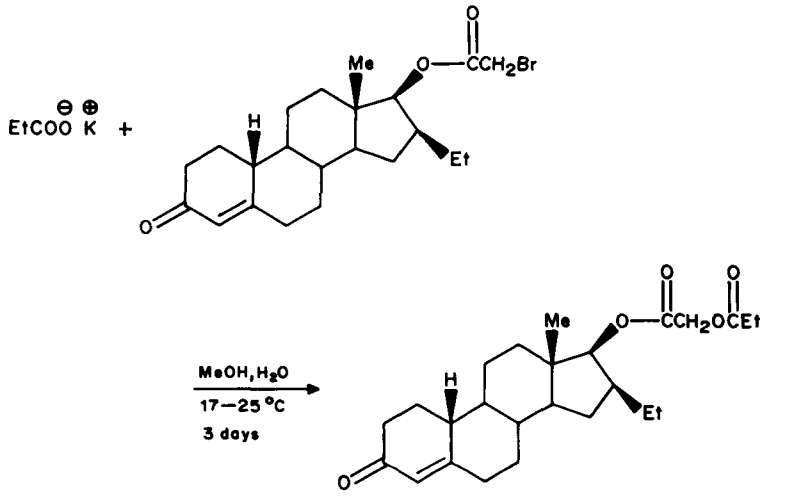
TABLE 91. Tetramethylethylenediamine catalyzed ester preparation[2004]

R^1	R^2X	Time	Temp. (°C)	TMEDA (mmol)	Product	Yield (%)
t-Bu	$PhCH_2Cl$	3 h	25	0	No reaction	—
t-Bu	$PhCH_2Cl$	3 h	25	0.75	*t*-$BuCOOCH_2Ph$	91
t-Bu	*n*-HexBr	21 h	25	0	*t*-BuCOOHex-*n*	Trace
t-Bu	*n*-HexBr	21 h	25	0.75	*t*-BuCOOHex-*n*	73
t-Bu	*n*-HexBr	30 min	83	0	*t*-BuCOOHex-*n*	Trace
t-Bu	*n*-HexBr	30 min	83	0.75	*t*-BuCOOHex-*n*	94
t-Bu	*n*-$C_7H_{15}Cl$	9 h	83	0	*t*-$BuCOOC_7H_{15}$-*n*	Trace
t-Bu	*n*-$C_7H_{15}Cl$	9 h	83	0.75	*t*-$BuCOOC_7H_{15}$-*n*	93
t-Bu	*n*-HexCHBrMe	24 h	83	0	*t*-BuCOOCH(Me)Hex-*n*	30
t-Bu	*n*-HexCHBrMe	24 h	83	0.75	*n*-BuCH=CHMe	78
t-Bu	PhCHClMe	7 h	83	0	*t*-BuCOOCH(Me)Ph	Trace
t-Bu	PhCHClMe	7 h	83	0.75	*t*-BuCOOCH(Me)Ph	92[a]
t-Bu	$Br(CH_2)_3Cl$	13 h	25	0	*t*-$BuCOO(CH_2)_3Cl$	Trace
t-Bu	$Br(CH_2)_3Cl$	13 h	25	0.75	*t*-$BuCOO(CH_2)_3Cl$ +	87.5
					t-$BuCCOO(CH_2)_3OOCBu$-*t*	5
t-Bu	$Br(CH_2)_3Br$	23 h	25	0	*t*-$BuCOO(CH_2)_3Br$	13.5
t-Bu	$Br(CH_2)_3Br$	23 h	25	0.75	*t*-$BuCOO(CH_2)_3Br$ +	4
					t-$BuCOO(CH_2)_3OOCBu$-*t*	
t-Bu	$Br(CH_2)_3Br$	15 min	83	0	*t*-$BuCOO(CH_2)_3Br$ +	39
					t-$BuCOO(CH_2)_3OOCBu$-*t*	10
t-Bu	$Br(CH_2)_3Br$	15 min	83	0.75	*t*-$BuCOO(CH_2)_3OOCBu$-*t*	94
t-Bu	$MeCOCH_2Cl$	30 min	25	0	*t*-$BuCOOCH_2COMe$	Trace
t-Bu	$MeCOCH_2Cl$	30 min	25	0.75	*t*-$BuCOOCH_2COMe$	95
t-Bu	$EtOCH_2Cl$	5 min	25	0	*t*-$BuCOOCH_2OEt$	100
Ph	$PhCH_2Cl$	3 h	25	0	No reaction	—

Ph	$PhCH_2Cl$	3 h	25	0.75	$PhCOOCH_2Ph$	89
Ph	*n*-HexBr	1 h	83	0	PhCOOHex-*n*	Trace
Ph	*n*-HexBr	1 h	83	0.75	PhCOOHex-*n*	94
PhCH(Et)	$PhCH_2Cl$	4 h	25	0	No reaction	—
PhCH(Et)	$PhCH_2Cl$	4 h	25	0.75	$PhCH(Et)COOCH_2Ph$	89
PhCH(Et)	*n*-HexBr	7 h	25	0	PhCH(Et)COOHex-*n*	Trace
PhCH(Et)	*n*-HexBr	7 h	25	0.75	PhCH(Et)COOHex-*n*	95
Ph_2CH	$PhCH_2Cl$	7 h	25	0	$Ph_2CHCOOCH_2Ph$	Trace
Ph_2CH	$PhCH_2Cl$	7 h	25	0.75	$Ph_2CHCOOCH_2Ph$	86
Ph_2CH	*n*-HexBr	45 min	83	0	$Ph_2CHCOOHex$-*n*	Trace
Ph_2CH	*n*-HexBr	45 min	83	0.75	$Ph_2CHCOOHex$-*n*	95
Ph_3C	$PhCH_2Cl$	12 h	25	0	$Ph_3CCOOCH_2Ph$	Trace
Ph_3C	$PhCH_2Cl$	12 h	25	0.75	$Ph_3CCOOCH_2Ph$	74
Ph_3C	*n*-HexBr	3 h	83	0.75	$Ph_3CCOOHex$-*n*	40
o-HOC_6H_4	$PhCH_2Cl$	4.5 h	83	0	*o*-$HOC_6H_4COOCH_2Ph$	~25
o-HOC_6H_4	$PhCH_2Cl$	4.5 h	83	0.75	*o*-$HOC_6H_4COOCH_2Ph$	88
o-HOC_6H_4	*n*-HexBr	3 h	83	0	*o*-$HOC_6H_4COOHex$-*n*	~30
o-HOC_6H_4	*n*-HexBr	3 h	83	0.75	*o*-$HOC_6H_4COOHex$-*n*	83
o-HOC_6H_4	$PhCOCH_2Br$	10 min	25	0	*o*-$HOC_6H_4COOCH_2COPh$	Trace
o-HOC_6H_4	$PhCOCH_2Br$	10 min	25	0.75	*o*-$HOC_6H_4COOCH_2COPh$	93
2,4,6-$Me_3C_6H_2$	$PhCH_2Cl$	7 h	25	0	2,4,6-$Me_3C_6H_2COOCH_2Ph$	Trace
2,4,6-$Me_3C_6H_2$	$PhCH_2Cl$	7 h	25	0.75	2,4,6-$Me_3C_6H_2COOCH_2Ph$	89
2,4,6-$Me_3C_6H_2$	*n*-HexBr	24 h	25	0	2,4,6-$Me_3C_6H_2COOHex$-*n*	~20
2,4,6-$Me_3C_6H_2$	*n*-HexBr	24 h	25	0.75	2,4,6-$Me_3C_6H_2COOHex$-*n*	91
2,4,6-$Me_3C_6H_2$	*n*-HexBr	15 min	83	0	2,4,6-$Me_3C_6H_2COOHex$-*n*	~30
2,4,6-$Me_3C_6H_2$	*n*-HexBr	15 min	83	0.75	2,4,6-$Me_3C_6H_2COOHex$-*n*	~85
2,4,6-$Me_3C_6H_2$	*n*-HexBr	30 min	83	0	2,4,6-$Me_3C_6H_2COOHex$-*n*	~55
2,4,6-$Me_3C_6H_2$	*n*-HexBr	30 min	83	0.75	2,4,6-$Me_3C_6H_2COOHex$-*n*	~95
2,4,6-$Me_3C_6H_2$	*p*-$BrC_6H_4COCH_2Br$	5 min	25	0	2,4,6-$Me_3C_6H_2COOCH_2COC_6H_4Br$-*p*	~95
2,4,6-$Me_3C_6H_2$	*p*-$BrC_6H_4COCH_2Br$	5 min	25	0.75	2,4,6-$Me_3C_6H_2COOCH_2COC_6H_4Br$-*p*	96

[a]Styrene (4%) is also formed.

5 minutes and then heated at 140 °C for 10 minutes. The resultant cake is ground to a powder and added to a flask containing the alkylating agent and the entire mixture shaken for 15 minutes. The results obtained using both methods with a variety of carboxylic acids and alkylating agents are reported in Table 92.



(980)

$$R^1COO\overset{\ominus}{O}\overset{\oplus}{K} + R^2X \xrightarrow{\text{TMEDA}} R^1COOR^2 \tag{981}$$

$$R^1COO\overset{\ominus}{O}\overset{\oplus}{K} + R^2X \xrightarrow[\text{shake, r.t.}]{\text{ammonium salt}} R^1COOR^2 \tag{982}$$

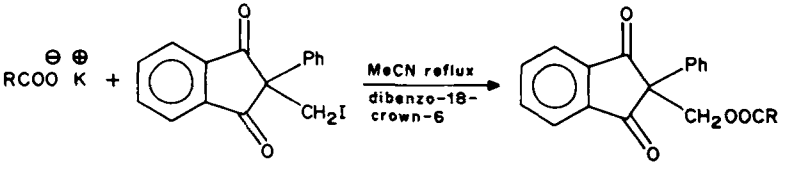
One example of the use of a nitrogen-containing compound as an alkylating agent in the esterification of carboxylic acids is illustrated by the reaction[2006] of tris (2-chloroethyl)amine with potassium carboxylates to produce the corresponding bis(2-chloroethyl)aminoethyl esters (equation 983).

$$RCOO\overset{\ominus}{O}\overset{\oplus}{K} + (ClCH_2CH_2)_3N \xrightarrow[\text{reflux}]{\text{EtOH}} RCOOCH_2CH_2N(CH_2CH_2Cl)_2 \tag{983}$$

80–92%

R = Ph, PhCH=CH, *o*-HOC_6H_4CH=CH, 2-Pyr, 3-Pyr, 4-Pyr

Using 18-crown-6-ethers (1,4,7,10,13,16-hexaoxacyclooctadecane) as a catalyst permits the condensation of a variety of potassium carboxylates and alkyl halides to produce structurally interesting esters. Examples of this approach include the reaction of several potassium carboxylates with 2-(iodomethyl)-2-phenyl-1,3-indanedione[2007] (equation 984),



R=Me, *p*-$O_2NC_6H_4$, 3-coumarinyl 39—93%

(984)

TABLE 92. Ammonium salt catalyzed ester preparation[2005]

R^1	Alkylating agent	Ammonium salt	Ratio of acid/alkyl. agent	Method[c]	Time (h)	Temp. (°C)	Yield (%)
Ph	EtBr	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	1.1:1	A or B	14	38	96
Ph	$PhCH_2Br$	Aliquat 336	1.1:1	A or B	8	25	92
Ph	$n\text{-}C_8H_{17}Br$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	1.1:1	A or B	2	85	92
Ph	$n\text{-}C_{16}H_{33}Br$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	1.1:1	A or B	24	50	90
Ph	$Br(CH_2)_4Br$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	2:1	A or B	1	85	84[a]
Ph	$Br(CH_2)_{12}Br$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$	2:1	A or B	24	85	88[a]
Ph	*i*-PrBr	Aliquat 336	1.1:1	A or B	24	60	91
Ph	*c*-HexBr	Aliquat 336	1.1:1	A or B	24	85	20
Ph	$Me(CH_2)_5CH(Br)Me$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	1.1:1	A or B	24	85	76
$p\text{-}O_2NC_6H_4$	$(EtO)_2SO_2$	Aliquat 336	1.1:1	A	24	25	91
$p\text{-}O_2NC_6H_4$	$PhCH_2Br$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$	1.1:1	A	8	25	93
$p\text{-}O_2NC_6H_4$	$n\text{-}C_8H_{17}Br$	Aliquat 336	1.1:1	A	3	85	92
$p\text{-}O_2NC_6H_4$	$n\text{-}C_{16}H_{33}Br$	Aliquat 336	1.1:1	A	40	85	93
$o\text{-}O_2NC_6H_4$	$(EtO)_2SO_2$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	1.1:1	A	6	25	93
$o\text{-}O_2NC_6H_4$	$PhCH_2Br$	Aliquat 336	1.1:1	A	8	25	89
$o\text{-}O_2NC_6H_4$	$n\text{-}C_8H_{17}Br$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	1.1:1	A	3	85	94
$o\text{-}O_2NC_6H_4$	$n\text{-}C_{16}H_{33}Br$	Aliquat 336	1.1:1	A	40	85	91
$p\text{-}HOC_6H_4$	$(MeO)_2SO_2$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	1:1	A	60	25	68

(*continued*)

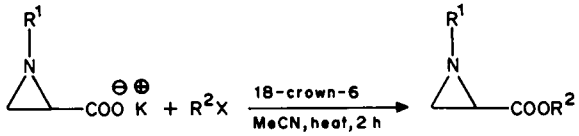
TABLE 92. (*continued*)

R^1	Alkylating agent	Ammonium salt	Ratio of acid/alkyl. agent	Method	Time (h)	Temp. (°C)	Yield (%)
p-HOC_6H_4	$PhCH_2Br$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	1:1	A	24	25	83
o-HOC_6H_4	$(MeO)_2SO_2$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	1:1	A	24	25	79
o-HOC_6H_4	$PhCH_2Br$	Aliquat 336	1:1	A	8	25	91
p-KOC_6H_4	$(MeO)_2SO_2$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$	1:2	A or B	24	25	83[b]
p-KOC_6H_4	$(EtO)_2SO_2$	Aliquat 336	1:2	A or B	15	60	81[b]
p-KOC_6H_4	$PhCH_2Br$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	1:2	A or B	24	40	81[b]
p-KOC_6H_4	*n*-$C_8H_{17}Br$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	1:2	A or B	80	85	81[b]
o-KOC_6H_4	MeI	Aliquat 336	1:2	A	24	25	80[b]
o-KOC_6H_4	$(EtO)_2SO_2$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	1:2	A	24	25	75[b]
o-KOC_6H_4	$PhCH_2Br$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	1:2	A	8	25	81[b]
p-An	$(MeO)_2SO_2$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	1.1:1	A	24	25	76
p-An	*n*-$C_8H_{17}Br$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	1.1:1	A	3	85	80
o-$KOOCC_6H_4$	$(EtO)_2SO_2$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	1:2	A	24	60	77[a]

o-$KOOCC_6H_4$	$H_2C{=}CHCH_2Br$	Aliquat 336	1:2	A	16	60	85[a]
o-$KOOCC_6H_4$	$PhCH_2Br$	Aliquat 336	1:2	A	16	60	85[a]
o-$KOOCC_6H_4$	*n*-$C_8H_{17}Br$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$	1:2	A	16	85	87[a]
o-$KOOCC_6H_4$	*n*-$C_{16}H_{33}CH(Br)Me$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$	1:2	A	24	85	72[a]
o-$KOOCC_6H_4$	*n*-$C_4H_9CH(Et)CH_2Br$	Aliquat 336	1:2	A	24	85	97[a]
m-$KOOCC_6H_4$	$(EtO)_2SO_2$	Aliquat 336	1:2	A	60	60	Trace[a]
m-$KOOCC_6H_4$	$H_2C{=}CHCH_2Br$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$	1:2	A	60	85	25[a]
m-$KOOCC_6H_4$	$PhCH_2Br$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	1:2	A	60	85	20[a]
m-$KOOCC_6H_4$	*n*-$C_8H_{17}Br$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	1:2	A	80	85	14[a]
p-$OHCC_6H_4$	$(EtO)_2SO_2$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$	1.1:1	A	20	40	91
p-$OHCC_6H_4$	*n*-$C_8H_{17}Br$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	1.1:1	A	24	85	92
p-$OHCC_6H_4$	*n*-$C_{16}H_{33}Br$	Aliquat 336	1.1:1	A	24	85	85
o-$OHCC_6H_4$	$(EtO)_2SO_2$	Aliquat 336	1.1:1	A	18	25	87
o-$OHCC_6H_4$	*n*-$C_8H_{17}Br$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	1.1:1	A	24	85	91
2-Fu	$(EtO)_2SO_2$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$	1.1:1	A	13	60	81
2-Fu	$PhCH_2Br$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$	1.1:1	A	15	25	91
2-Fu	*n*-$C_8H_{17}Br$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	1.1:1	A	24	85	88
2-Fu	*n*-$C_{16}H_{33}Br$	$(t\text{-Bu})_4\overset{+}{N}\overset{-}{Br}$ or Aliquat 336	1.1:1	A	24	85	89

[a] Product is diester.
[b] Product is alkoxy substituted ester.
[c] For methods A and B see text.

the reaction of potassium substituted aziridine carboxylates with alkyl halides[2008] (equation 985), condensation of various potassium carboxylates with pentafluorobenzyl bromide[2009] (equation 986) and reaction of potassium carboxylates with chloromethyl methyl sulfide[2010] (equation 987). This latter reaction affords a convenient means of protecting carboxylic acids which can then be deprotected[2010] by reaction with mercuric chloride followed by hydrogen sulfide.



(985)

R^1	RX	Yield (%)
Me_3C	$BrCH_2CH{=}CH_2$	77
Me_3C	$BrCH_2CH{=}CHCOOMe$	84
Me_3C	$BrCH_2CH{=}CHCH_2CN$	88
Me_3C	$BrCH_2CH{=}C(CH_2)_2CH{=}CMe_2$ (Me)	84
Me_3C	$BrCH_2C{\equiv}CH$	70
Me_3C	$ClCH_2COMe$	84
Me_3C	$Cl(CH_2)_2NEt_2$	84
Me_3C	BrCH(OMe)COOMe	58
Me_2C	$BrCH_2C{\equiv}CH$	74
PhCH(Me)	$BrCH_2CH{=}CH_2$	84
Me_3C	$Br(CH_2)_3Br$	70[a]
Me_3C	$Br(CH_2)_4Br$	48[a]
Me_3C	$BrCH_2CH{=}CHCH_2Br$ (*trans*)	77[a]
Me_3C	*o*-$BrCH_2C_6H_4CH_2Br$	52[a]

[a]Diester formed as product.

$$RCOO^{\ominus}K^{\oplus} + C_6F_5CH_2Br \xrightarrow[K_2CO_3,\ \text{shake}]{\text{18-crown-6}} RCOOCH_2C_6F_5 \qquad (986)$$

R = Me, Et, *n*-Pr, *n*-Bu, Me_2CHCH_2, *n*-C_5H_{11}, *n*-C_7H_{15}, *n*-$C_8H_{17}CH{=}CH(CH_2)_7$ (*cis*), MeCH(OH), $PhCONHCH_2$, Ph, PhCH(OH), $PhCH_2$, $Ph(CH_2)_2$, indoleacetic, *m*-HOC_6H_4, *p*-HOC_6H_4, *m*-$HOC_6H_4CH(OH)$, *p*-$HOC_6H_4CH(OH)$, homovanillic, 3,4-$(HO)_2C_6H_3CH_2$

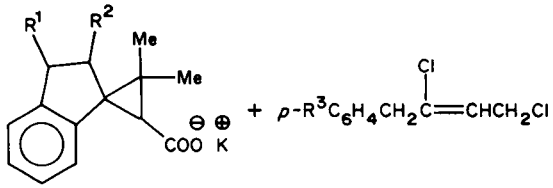
$$RCOO^{\ominus}K^{\oplus} + ClCH_2SCH_3 \xrightarrow[NaI,\ C_6H_6]{\text{18-crown-6}} RCOOCH_2SCH_3 \qquad (987)$$

R = Ph	PhCH=CH	2,4,6-$Me_3C_6H_2$	MeC	PhCH(OTHP)[a]
% Yield = 90	97	85	85	88

[a]Tetrahydropyranyl ether of OH function.

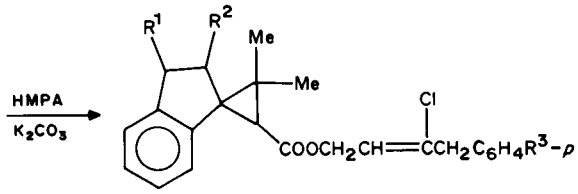
Using HMPA as a condensing agent[2011] 2,2-dimethyl-4,5-benzospiro[2.4]-heptane-1-

and hepta-4,6-diene-1-carboxylic acid esters (equation 988) have been prepared from potassium carboxylates.

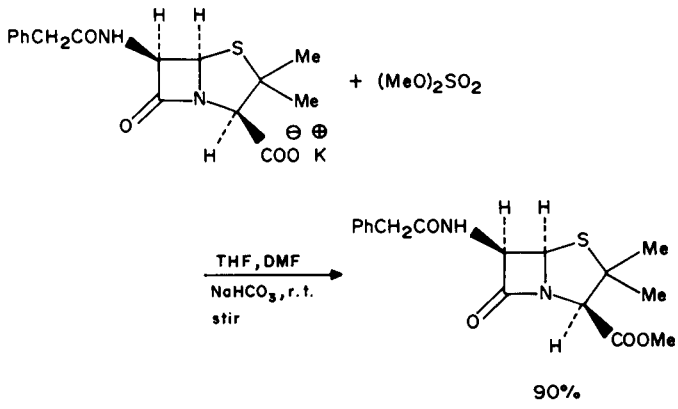


$R^1=R^2=H$, double bond
$R^3=H, Me, Cl$

(988)



The use of dimethyl sulfate as an alkylating agent in the preparation of methyl esters from potassium carboxylates is represented in the recent literature[2012] by the esterification of potassium (or sodium) benzylpenicillinate (equation 989).



(989)

Many of the alkylating agents used in conjunction with the sodium carboxylates are the same or similar to the alkylating agents used to prepare esters from the potassium carboxylates. Thus, reaction of sodium carboxylates with alkyl chlorides in a solvent at 60–90 °C in the presence of benzyl tri-(*n*-butyl)ammonium chloride produces[2013] the corresponding esters (equation 990) in 94–100% yields. Solvents such as acetone and DMF are reported[2013] to give excellent yields from this reaction with a high initial rate of formation of the esters, while a solvent such as benzene is reported to produce poor results.

$$R^1COO^{\ominus}\overset{\oplus}{N}a + R^2Cl \xrightarrow[\text{solvent, 60–90 °C}]{PhCH_2\overset{\oplus}{N}(Bu\text{-}n)_3\ \overset{\ominus}{Cl}} R^1COOR^2 \qquad (990)$$

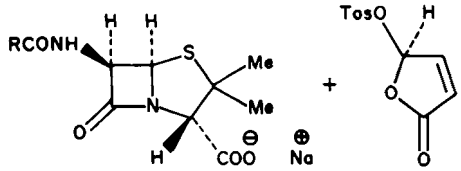
R^1 = Me, CH_2=C(Me), Ph, $NaOOCC_6H_4$ (diester formed)
R^2 = $PhCH_2$, CH_2CHCH_2, *n*-Bu, $(MeO)_3SiCH_2$, $HOCH_2CH_2$, CH_2—CH_2—CH_2 (O)

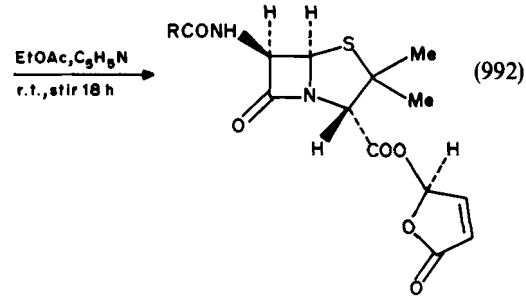
18-Crown-6 ether is used as a catalyst in the esterification of sodium carboxylates (or other acid salts)[2014] as, e.g., in the condensation of sodium benzoate with phenyl *n*-butyl methylsilyl chloride (equation 991).

$$PhCOO^{\ominus}\overset{\oplus}{N}a + (n\text{-Bu})SiClMePh \xrightarrow[\text{r.t., 3 h}]{\text{THF, 18-crown-6}} PhCOOSiMePh(n\text{-Bu}) \qquad (991)$$

other salts used: MeCOOK, $(PhCOO)_2Mg$ and $(CH_3COO)_3Al$
other silyl halides used: $Me_3CSiClMe_2$, CH_2=CHSiClMePh, and $PhCH_2CH_2SiClMe_2$

Condensation of the sodium (or other salts) or penicillins with arylsulfonate esters of 3-hydroxylactones (equation 992) or substituted 3-halolactones (equation 993) produces[2015] a variety of lactonyl esters of penicillins in yields ranging from 13 to 91%.



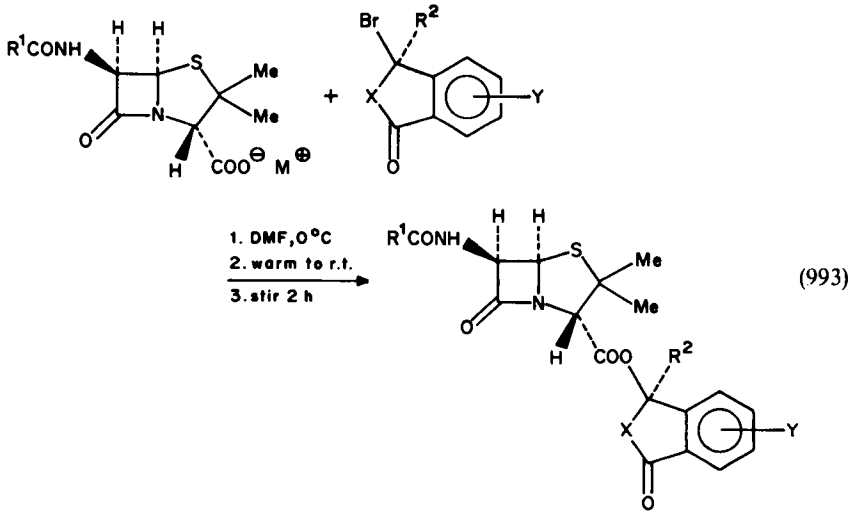


(992)

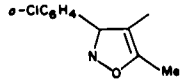
R =	$PhCH_2$	D-$PhCH(NH_2)$
% Yield =	14	30

At least one report of the use of phosphorus-containing alkylating agents in esterification of sodium carboxylates has appeared in the literature. This report involves the preparation[2016] of the 2,2,2-trichloroethyl ester of penicillin G by reaction of the sodium salt of penicillin G with bis(2,2,2-trichloroethoxy) chlorophosphonate (equation 994).

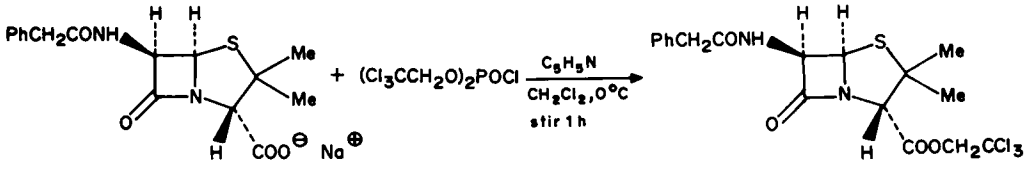
Finally, sodium carboxylates have also been used in the preparation of methylthiomethyl esters by a Pummerer-like reaction[2017] involving the condensation of *t*-butyl bromide activated dimethyl sulfoxide with sodium carboxylates in the presence of a mild base (equation 995).



(993)

R^1	R^2	M	X	Y	Yield (%)[a]
	H	Na	O	H	91
$PhOCH_2$	H	Na	O	H	60
$PhCH_2$	H	K	O	H	45[b]
D-$PhCH(NH_2 \cdot HCl)$	H	K	O	H	65[c]
$PhCH_2$	H	Na	O	6-OMe	34
D-$PhCH(NH_2 \cdot HCl)$	H	Na	O	6-OMe	51[c]
$PhCH_2$	H	Na	O	5,6-$(OMe)_2$	41
D-$PhCH(NH_2 \cdot HCl)$	H	Na	O	5,6-$(OMe)_2$	29[c]
D-$PhCH(NH_2 \cdot HCl)$	H	Na	O	4,5,6-$(OMe)_3$	70[c]
D-$PhCH(NH_2 \cdot HCl)$	H	Na	O	6-Cl	47[c]
D-$PhCH(NH_2 \cdot HCl)$	H	Na	O	6-Br	44[c]
$PhOCH_2$	Me	K	O	H	32
$PhCH_2$	Ph	Na	O	H	25
$PhCH_2$	H	Na	S	H	13

[a] All penicillins are amorphous and obtained as mixtures epimeric at C_3 in the lactone function.
[b] 1:1 epimeric mixture.
[c] Yield in esterification and deprotection.



(994)

$$Me_2SO + t\text{-}BuBr \rightleftharpoons [Br^{\ominus}Me_2\overset{\oplus}{S}{-}OBu\text{-}t] \xrightleftharpoons{RCOO^{\ominus}Na^{\oplus}} [Br^{\ominus}Me_2\overset{\oplus}{S}OC(=O)R]$$

$$\xrightarrow{base} [CH_2{=}S(Me){-}OC(=O)R] \longrightarrow RCOOCH_2SMe \qquad (995)$$

Acid	Product	Yield (%)
MeCOOH	$MeCOOCH_2SMe$	95
PhCOOH	$PhCOOCH_2SMe$	98
Me_2CHCH_2COOH	$Me_2CHCH_2COOCH_2SMe$	95
$Me_2C{=}CHCOOH$	$Me_2C{=}CHCOOCH_2SMe$	95
$HOOC(CH_2)_4COOH$	$(CH_2)_4(COOCH_2SMe)_2$	97
$PhCH{=}CHCOOH$ (*cis*)	$PhCH{=}CHCOOCH_2SMe$	95
$CH_2{=}CH(CH_2)_7COOH$	$CH_2{=}CH(CH_2)_7COOCH_2SMe$	90
PhCH(OH)COOH (*R*, *S*)	$PhCH(OH)COOCH_2SMe$	80
(L)-3-Indolyl-CH_2CHCOOH | $NHCOOCH_2Ph$	3-Indolyl-CH_2CHCOOCH_2SMe | $NHCOOCH_2Ph$	94
(L)-$HOCH_2$CHCOOH | $NHCOOCH_2Ph$	$HOCH_2CHCOOCH_2SMe$ | $NHCOOCH_2Ph$	88
(L)-MeCHCOOH | $NHCOOCH_2Ph$	$MeCHCOOCH_2SMe$ | $NHCOOCH_2Ph$	98
(L)-$PhCH_2$CHCOOH | $NHCOOCH_2Ph$	$PhCH_2CHCOOCH_2SMe$ | $NHCOOCH_2Ph$	95
(L)-$PhCH_2$CHCOOH | $NHCOOCMe_3$	$PhCH_2CHCOOCH_2SMe$ | $NHCOOCMe_3$	90
(L)-$PhCH_2$CHCOOH | NHNPS[a]	$PhCH_2CHCOOCH_2SMe$ | NHNPS[a]	85
(L)-$PhCH_2$CHCOOH | NHFOR[b]	$PhCH_2CHCOOCH_2SMe$ | NHFOR[b]	80
(L)-$PhCH_2$CHCOOH | NHPHT[c]	$PhCH_2CHCOOCH_2SMe$ | NHPHT[c]	90
(L)-$PhCH_2$CHCOOH | NHTFA[d]	$PhCH_2CHCOOCH_2SMe$ | NHTFA[d]	80

[a] NPS = α-nitrophenylsulfenyl
[b] FOR = formyl
[c] PHT = phthalyl
[d] TFA = trifluoroacetyl

Several recent examples of the use of ammonium salts of carboxylic acids in the preparation of esters are presented in this section.

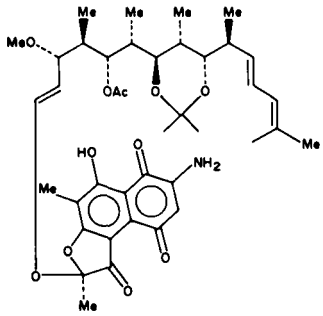
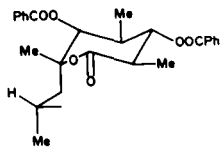
Reaction of 2-thiopyridyl chloroformate (prepared from phosgene and 2-pyridinethiol

in 96% yield) with the triethylammonium salts of carboxylic acids produces[2018] the corresponding 2-pyridinethiol carboxylic esters. Two procedures were used to perform the reaction as illustrated in equation 996.

$$RCOO^{\oplus}\overset{\ominus}{N}HEt_3 \xrightarrow{\text{Procedure A or B}} \text{2-PyrSC(=O)R} + Et_3NHCl + CO_2 \qquad (996)$$

Procedure A: 1) ether, 0 °C; 2) chloroformate, CH_2Cl_2, stir 0.5 h; 3) ether, $MgSO_4$

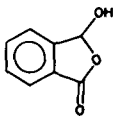
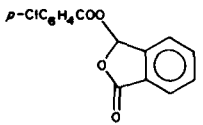
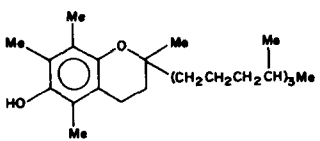
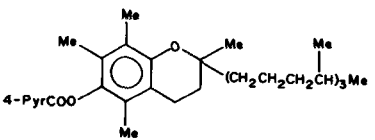
Procedure B: 1) CH_2Cl_2, 0 °C; 2) chloroformate, CH_2Cl_2, stir 0.5 h; 3) 10% $NaHCO_3$, 5% HCl wash

R	% Yield	
	Procedure A	Procedure B
Ph	98	100
c-Hex	100	100
	95	97
$MeCOCH_2CH_2$	98	95
	—	95
	—	97

Triethylammonium carboxylates are also transformed into esters by reaction[2019] with alcohols catalyzed with *N*,*N*-bis(2-oxo-3-oxazolidinyl) phosphordiamic chloride (equation 997 and Table 93).

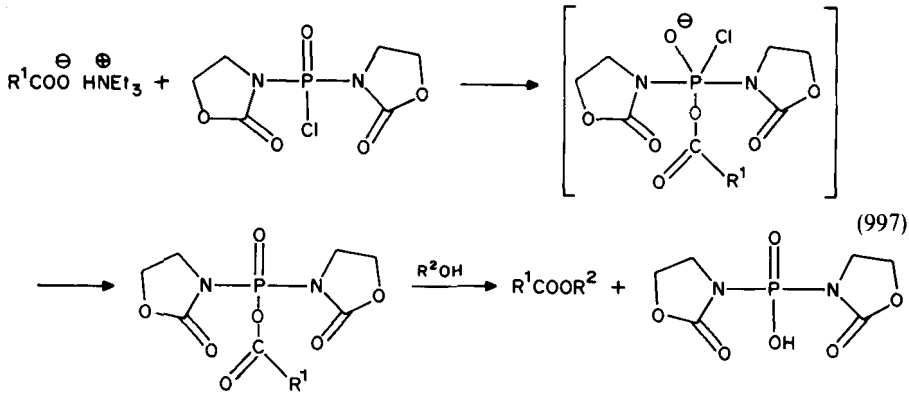
Two electrochemical esterification procedures using quaternary ammonium salts of carboxylic acids have appeared recently. In the first report is described[2020] a one-pot preparation of the quaternary ammonium salts of the carboxylic acids and their subsequent esterification, both conversions taking place in a cathode chamber (equation 998). Two methods were used to effect this procedure: Method A, which involved the addition of the alkylating agent to the catholyte before the electrolytic current was turned on, and after electrolysis the catholyte was allowed to stand at room temperature for one hour; and, Method B, which involved addition of the alkylating agent to the catholyte after the electrolytic current was turned off.

TABLE 93. *N,N*-Bis(2-oxo-3-oxazolidinyl)phosphoridiamic chloride catalyzed ester preparation[2019]

R^1	R^2	Solvent	Rx. time	Product	Yield (%)
$3,5\text{-}(O_2N)_2C_6H_3$	t-BuOH	MeCN	Reflux, 1 h	$3,5\text{-}(O_2N)_2C_6H_3COOBu\text{-}t$	61.2
$p\text{-}ClC_6H_4$	$PhCH_2OH$	MeCN	Reflux, 1.5 h	$p\text{-}ClC_6H_4COOCH_2Ph$	100
$3,5\text{-}(O_2N)_2C_6H_3$	$PhCH_2OH$	MeCN	Reflux, 1 h	$3,5\text{-}(O_2N)_2C_6H_3COOCH_2Ph$	83
$3,5\text{-}(O_2N)_2C_6H_3$	Me_2CHOH	$MeCONMe_2$	r.t., 1 h	$3,5\text{-}(O_2N)_2C_6H_3COOCHMe_2$	88.2
$p\text{-}ClC_6H_4$		MeCN	Reflux, 1.5 h		73.5
3-Pyr	$PhCH_2OH$	Cl_2CH_2	r.t., 1 h	3-PyrCOOCH_2Ph	100
4-Pyr		Cl_2CH_2	r.t., 1.5 h		75

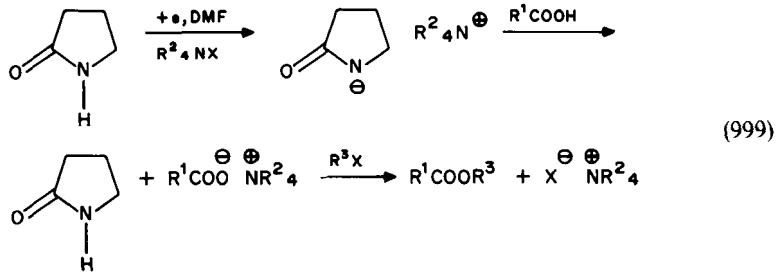
$$R^1COOH \xrightarrow[\substack{Et_4\overset{\oplus}{N}\overset{\ominus}{T}s,\ DMF\\ platinum\ electrode\ in\\ divided\ H\text{-}cell}]{e - \frac{1}{2}H_2} R^1COO\overset{\ominus}{N}\overset{\oplus}{E}t_4 \xrightarrow[X = halide\ or\ OTs]{R^2X} R^1COOR^2 + \overset{\ominus}{X}\overset{\oplus}{N}Et_4 \qquad (998)$$

Acid	Alkylating agent	Method	Product	Yield (%)
MeCOOH	*n*-BuCl	A	MeCOOBu-*n*	24
MeCOOH	*n*-BuBr	A	MeCOOBu-*n*	60
MeCOOH	*n*-BuI	A	MeCOOBu-*n*	25
MeCOOH	*n*-BuOTs	A	MeCOOBu-*n*	48
MeCOOH	*n*-BuCl	B	MeCOOBu-*n*	27
MeCOOH	*n*-BuBr	B	MeCOOBu-*n*	68
MeCOOH	*n*-BuI	B	MeCOOBu-*n*	96
n-PrCOOH	EtI	B	*n*-PrCOOEt	96
n-PrCOOH	EtOTs	A	*n*-PrCOOEt	70
PhCOOH	MeI	B	PhCOOMe	80
PhCOOH	EtI	B	PhCOOEt	83
PhCOOH	MeOTs	A	PhCOOMe	75
$HOOC(CH_2)_4COOH$	MeI	B	$(CH_2)_4(COOMe)_2$	24–80
PhCH(OH)COOH	EtI	B	PhCH(OH)COOEt	90
$ClCH_2COOH$	MeI	B	$ClCH_2COOMe$	42
MeCH=CHCOOH	MeI	B	MeCH=CHCOOMe	77
HC≡CCOOH	MeI	B	HC≡CCOOMe	58
3-PyrCOOH	MeI	B	3-PyrCOOMe	70

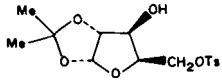
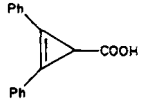


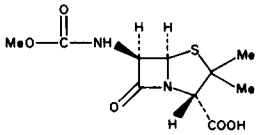
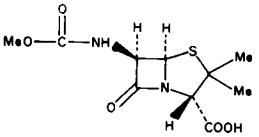
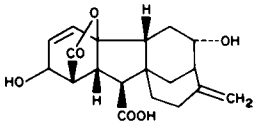
(997)

In the second report, the electroreduction of 2-pyrrolidone in DMF in the presence of tetraalkylammonium salts produces[2021] a highly efficient base which can be used in the esterification of carboxylic acids (equation 999). The mechanism involves initial formation of the corresponding ammonium carboxylates followed by intermolecular (ester formation) or intramolecular (macrolide formation) reaction with alkyl halides.



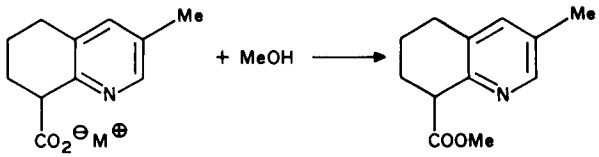
(999)

Acid	Alkylating agent	R^{2a}	Yield (%)
$Me(CH_2)_8COOH$	*s*-BuCl	—	83
$Me(CH_2)_8COOH$	*o*-$BrCH_2C_6H_4COOMe$	—	80
$Me(CH_2)_8COOH$		—	94
$(CH_2)_3COOH$	$PhCOCH_2Br$	—	92[b]
1-AdCOOH	*i*-PrI	—	96
$HO(CH_2)_{11}COOH$	$PhCH_2Br$	—	> 99
$PhCH_2CH_2COOH$	$ClCH_2OMe$	—	> 99
p-$HOOCC_6H_4CH_2CH_2COOH$	*i*-PrI	—	92[b]
PhCH=CHCOOH (*trans*)	*i*-PrI	—	77
PhCH=CHCOOH (*trans*)	$MeSCH_2Cl$	—	95
	$PhCH_2Br$	—	99

Acid	Alkylating agent	R^{2a}	Yield (%)
o-ClC_6H_4COOH	$PhCH_2Br$	—	> 99
p-ClC_6H_4COOH	$PhCH_2Br$	—	> 99
p-AnCOOH	$PhCH_2Br$	—	> 99
2,4,6-$Me_3C_6H_2COOH$	*i*-PrI	—	> 99
PhCOOH	$CH_2{=}CHCH_2Br$	—	96
MeCHCOOH | $NHCOOCH_2Ph$	MeI	—	90
	$PhCH_2Br$	Et	86
	*p*-$MeOOCC_6H_4CH_2Br$	Et	65
	EtI	Et	77

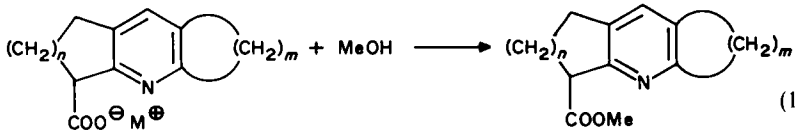
[a] R^2 = Et, *n*-Bu, or *n*-C_8H_{17} but is unspecified for most reactions.
[b] Product was the corresponding diester.

Treatment of the lithio or halomagnesio salts of 5,6,7,8-tetrahydro-3-methylquinoline-8-carboxylate (equation 1000) and its analogues (equations 1001 and 1002) with methanol affords[2022] the corresponding methyl esters. The salts of these acids were prepared[2022] by



(1000)

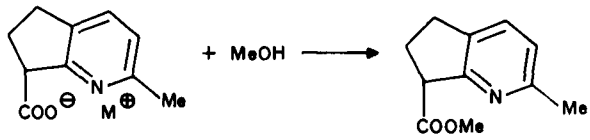
M=MgBr; Li
%Yield= 58;42–44



(1001)

n = 2; 1; 3
m = 4; 3; 5
M=MgBr and Li

treatment of the unsubstituted precursors with *i*-propylmagnesium bromide or phenyllithium in ether or with *n*-butyllithium in hexane, to produce the lithio or halomagnesio derivatives, which were then carboxylated by carbon dioxide.



(1002)

*3. *Alcoholysis of acyl halides*

Preparation of esters by the reaction of acid chlorides with alcohols is represented by a number of recent references and illustrates the continued usefulness of this approach to the preparation of carboxylic acid esters. Since most reactions of this kind are fairly simple and involve the condensation of an acid chloride with an alcohol (equation 1003), recent examples of esters which have been prepared in this manner are recorded in Table 94 without further discussion.

$$R^1COCl + R^2OH \xrightarrow{\text{Conditions}} R^1COOR^2 \tag{1003}$$

Zinc chloride has been found to be an effective catalyst for the condensation of acid chlorides with alcohols[2043] and thiols[2043] (equation 1004) to produce esters, and for the condensation of acid chlorides with aldehydes to produce[2044] (1-haloalkyl) esters (equation 1005).

$$R^1COCl + R^2XH \xrightarrow[\text{r.t., 0.1–6 h}]{\text{MeCN, } ZnCl_2} R^1COOR^2 \quad 76\text{–}99\% \tag{1004}$$

with X = O:

R^1 = Me_3C, *n*-C_7H_{15}, mesityl, Ph, *p*-$MeOC_6H_4$
R^2 = mesityl, *c*-C_6H_{11}, $Me(CH_2)_5CH(Me)$, *β*-naphthyl, $PhCH_2$, Me, Et, Ph

with X = S:

R^1 = as above
R^2 = Me_3C, Ph, *n*-Bu

$$R^1COCl + R^2CHO \xrightarrow[42\,^\circ C]{ZnCl_2} R^1COOCHClR^2 \tag{1005}$$

R^1 = Me, Me, Me, Me, Me, Me
R^2 = Me, Me_2CH, Me_3C, Ph, *p*-Tol, *p*-An,

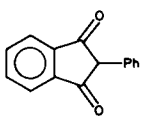
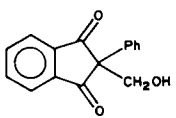
R^1 = Me, Me, Me, Me
R^2 = *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-FC_6H_4, *p*-$O_2NOC_6H_4$

R^1 = Ph, Ph, Ph, Ph, *p*-ClC_6H_4
R^2 = *t*-Bu, Ph, *p*-Tol, *p*-$O_2NC_6H_4$, *t*-Bu

R^1 = *p*-ClC_6H_4, *p*-ClC_6H_4, *p*-MeC_6H_4, *p*-Tol
R^2 = Ph, *p*-Tol, *t*-Bu, Ph

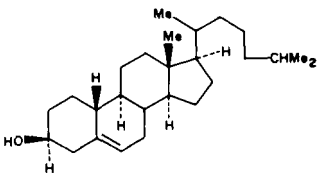
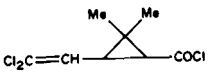
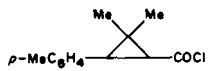
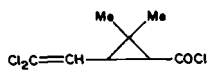
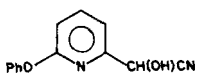
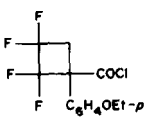
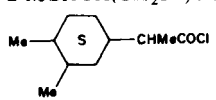
R^1 = *p*-Tol, *p*-An, *p*-An, *p*-An
R^2 = *p*-Tol, *t*-Bu, Ph, *p*-Tol

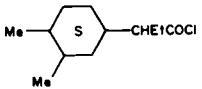
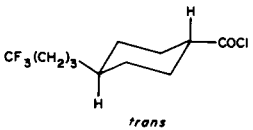
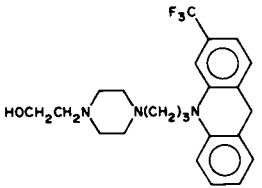
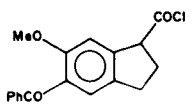
TABLE 94. Preparation of esters by reaction of acid chlorides with alcohols or phenols

Acid chloride	Alcohol or phenol	Conditions	Yield (%)	Reference
HCOCl	MeOH	Me_2CO, 2 h	62	2023
RCOCl R = Me, Et, *n*-Pr, and *n*-Bu	1-PipCH_2OH	—	49–80	2024
RCOCl R = Me, Et, *n*-Pr, and *n*-Bu	*N*-Morpholinyl CH_2OH	—	49–80	2024
$Me_2CRCOCl$ R = *n*-alkyl C_1–C_6	$H_2C{=}CHCH_2OH$	100 °C	85–95	2025
MeEtCRCOCl R = *n*-alkyl C_2–C_5	$H_2C{=}CHCH_2OH$	100 °C	85–95	2025
$H(CF_2)_nCOCl$ *n* = 1,2 or 4	ROH R = Me, Et	Reflux	—	2026
MeCOCl	*i*-PrCH_2OH	*a*	72	2027
MeCOCl	$H_2C{=}CHCH_2OH$	*a*	69	2027
MeCOCl	*t*-BuOH	*b*	79	2027
MeCOCl	Me_2CEtOH	*b*	80	2027
$PhCH_2COCl$	*t*-BuOH	*b*	75	2027
EtCOCl	$H_2C{=}CHCH_2OH$	*a*	69	2027
EtCOCl	*t*-BuOH	*b*	84	2027
EtCOCl	$Me_2C(Et)OH$	*b*	78	2027
F_3CCOCl	PhOH	Me_2CO, 2 h	70	2023
RCOCl R = alkyl or aryl		THF, Et_3N	4–93	2028[c]
RCOCl R = Me, *p*-$O_2NC_6H_4$ or 3-coumarinyl		THF, Et_3N	—	2028[c]

(*continued*)

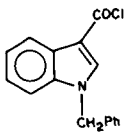
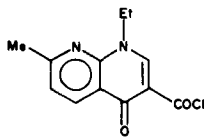
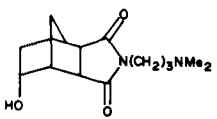
TABLE 94. (*continued*)

Acid chloride	Alcohol or phenol	Conditions	Yield (%)	Reference
$Me(CH_2)_{14}COCl$		Hexane, $PhCH_2NHCONMe_2$, reflux 4 h	—	2029
	$C_6F_5CH_2OH$	—	100	2030
	*m*-$PhOC_6H_4CH(OH)CN$	—	—	2031
		Et_3N	—	2032
	*m*-$PhOC_6H_4CH_2OH$	—	—	2033
2-MCHCHMeCOCl[f]	$Et_2NCH_2CH_2OH$	Reflux, 6 h	45	2034
2-MCHCHEtCOCl[f]	$Et_2NCH_2CH_2OH$	Reflux, 6 h	—	2034
2-MCHCH(*i*-Pr)COCl[f]	$Et_2NCH_2CH_2OH$	Reflux, 6 h	—	2034
2-MCHCH($CH_2CH{=}CH_2$)COCl[f]	$Et_2NCH_2CH_2OH$	Reflux, 6 h	—	2034
2-MCHCH(CH_2Ph)COCl[f]	$Et_2NCH_2CH_2OH$	Reflux, 6 h	—	2034
	$Et_2NCH_2CH_2OH$	Reflux, 6 h	—	2034

	$Et_2NCH_2CH_2OH$	Reflux, 6 h	—	2034
	*p*-HOC_6H_4CN	C_5H_5N, 40 C, 2 h	62	2035
1-AdCOCl		Et_3N, C_6H_6 reflux, 6 h	—	2036[d]
H_2NCH_2COCl	2,4,5-$Cl_3C_6H_2OH$	—	41	2037
PhCOCl	MeOH	—	82	2037
PhCOCl	*n*-C_4H_9OH	*a*	90	2027
PhCOCl	Me_2CHCH_2OH	*a*	91	2027
PhCOCl	$H_2C{=}CHCH_2OH$	*a*	70	2027
PhCOCl	$PhCH_2OH$	*a*	85	2027
PhCOCl	PhCH(Me)OH	*a*	65	2027
PhCOCl	*o*-$H_2NC_6H_4OH$	—	73	2037[e]
o-$MeCOOC_6H_4COCl$	MeOH	—	45	2037
p-$F_3C(CH_2)_2C_6H_4COCl$	*p*-HOC_6H_4CN	C_5H_5N, 40 °C, 2 h	68	2035
p-$F_3C(CH_2)_3C_6H_4COCl$	*p*-HOC_6H_4CN	C_5H_5N, 40 °C, 2 h	72	2035
p-$O_2NC_6H_4COCl$	MeOH	Me_2CO, 2 h	62	2023
2-NaphCOCl	$HC{\equiv}CCH_2OH$	C_5H_5N	—	2038
	MeOH	THF, −5 °C	—	2039

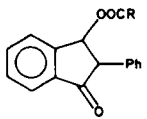
(*continued*)

TABLE 94. (*continued*)

Acid chloride	Alcohol or phenol	Conditions	Yield (%)	Reference
	ROH R = $Me_2NCH_2CH_2$, $Et_2NCH_2CH_2$, $Me_2NCH_2CH_2CH_2$, 2-Morpholinyl CH_2CH_2, 2-PipCH_2CH_2	—	51–78	2040
	ROH R = C_2–C_{12} alkyl, $HOCH_2CH_2$, PhCH(COOEt), Ph, XC_6H_4, *m*-$CF_3C_6H_4$	Et_3N	—	2041
2-Quinolyl COCl		C_5H_5N, 23 °C stir 72 h	—	2042

[a] Phase transfer conditions either $(n\text{-Bu})_4N^{\oplus}Cl^{\ominus}$, NaOH or KOH, H_2O, solvent, 0 °C, stir 5–10 min.

[b] CH_2Cl_2, anhy. Na_2CO_3, $PhCH_2\overset{\oplus}{N}Et_3Cl^-$ stir with heating 3 h.

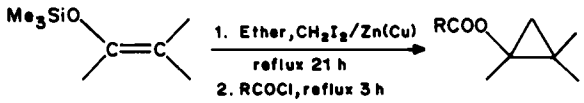
[c] Product was 

[d] Also prepared using Et_3N in toluene with reflux 4 h or in xylene reflux 2 h.

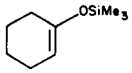
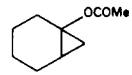
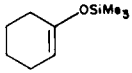
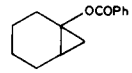
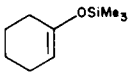
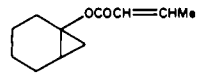
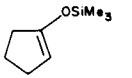
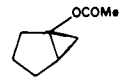
[e] Both amine and hydroxy groups are benzoylated, product is *o*-$PhCONHC_6H_4OOCPh$.

[f] 2-MCH ≡ 2-Methylcyclohexyl 

Several esterification reactions involve the condensation of acid halides with trimethylsilyl ethers, in place of alcohols. An interesting example[2045] of this approach involves the initial reaction of silyl enol ethers with methylene iodide in the presence of a zinc–copper couple (Simmons–Smith reagent) to produce *in situ* the cyclopropyl analog of the starting material, which is not isolated but is allowed to react directly with the acid chloride to produce the cyclopropyl ester (equation 1006).

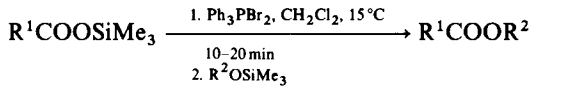


(1006)

Enol ether	Acid halide	Product	% Yield
	MeCOCl		65
	PhCOCl		43, 70[a]
	MeCH=CHCOCl		58
	MeCOCl		70
$PhC(OSiMe_3)=CH_2$	MeCOCl		48

[a]With two equivalents of benzyl chloride.

Another interesting example of this approach to ester formation involves the reaction[2046] of trimethylsilyl esters of carboxylic acids with triphenylphosphine dibromide to produce the intermediate acid bromide *in situ*, which is not isolated, but is allowed to react directly with the trimethylsilyl ethers to produce the corresponding esters (equation 1007).



(1007)

		Reaction conditions		
R^1	R^2	(°C)	Time (h)	Yield (%)
Et	Ph	15	15	84
$H_2C=CMe$	*i*-Pr	15	15	75
MeCH=CH	Et	15	15	70
$Me_2C=CH$	Et	15	15	90

R^1	R^2	Reaction conditions (°C)	Time (h)	Yield (%)
Ph	Me	15	15	85
$PhCH_2CH_2$	$PhCH_2$	15	15	71
PhCH=CH	Et	15	10	93
$PhCH(COOSiMe_3)_2$	Et	15	15	91
$3,5\text{-}(O_2N)_2C_6H_3$	Me	10	10	98

Reaction of acyl halides with 4-(di-*n*-butylchlorostannoxy)-1-alkenes at room temperature produces[2047] excellent yields of 1-alken-4-yl esters via a transalkoxylation reaction between the two reactants (equation 1008). When 92:8 percent mixtures of 4-(di-*n*-butylchlorostannoxy)-1-hexyne to 1,2-hexadiene were similarly treated[2047], mixtures of the corresponding esters were obtained which retained the original percent composition of the mixture (equation 1009).

$$R^1COCl + R^2CHCH_2CH{=}CH_2 \xrightarrow[2.\ \text{aq. } NaHCO_3]{1.\ \text{r.t., 20 min}} R^2CHCH_2CH{=}CH_2 \quad (1008)$$
$$\qquad\qquad\quad | \qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\quad OSn(n\text{-}Bu)_2Cl \qquad\qquad\qquad\quad OCOR^1$$

R^1	R^2	Product (in equation 1008)	Yield (%)
Me	Et	$R^2 = Et$, $R^1 = Me$	~100
Et	Et	$R^2 = Et$, $R^1 = Et$	98
CH_2Cl	Et	$R^2 = Et$, $R^1 = CH_2Cl$	91
n-Pr	Et	$R^2 = Et$, $R^1 = n\text{-}Pr$	95
t-Bu	Et	$R^2 = Et$, $R^1 = t\text{-}Bu$	80
t-$BuCH_2$	Et	$R^2 = Et$, $R^1 = CH_2Bu\text{-}t$	85
$CH_2{=}CH$	Et	$R^2 = Et$, $R^1 = CH_2CH_2$	91
(*E*)-MeCH=CH	Et	$R^2 = Et$, $R^1 = (E)\text{-}CH{=}CHMe\text{-}(E)$	98
Me	Me	$R^1 = R^2 = Me$	87
Me	Me_2CH	$R^2 = Me_2CH$, $R^1 = Me$	92
Me	*t*-Bu	$R^2 = t\text{-}Bu$, $R^1 = Me$	89
Me	(*E*)-MeCH=CH	$R^2 = (E)\text{-}MeCH{=}CH$, $R^1 = Me$	91
$(MeCO)_2O$[a]	Et	$R^2 = Et$, $R^1 = Me$	90

[a]Acetic anhydride used in place of acetyl chloride.

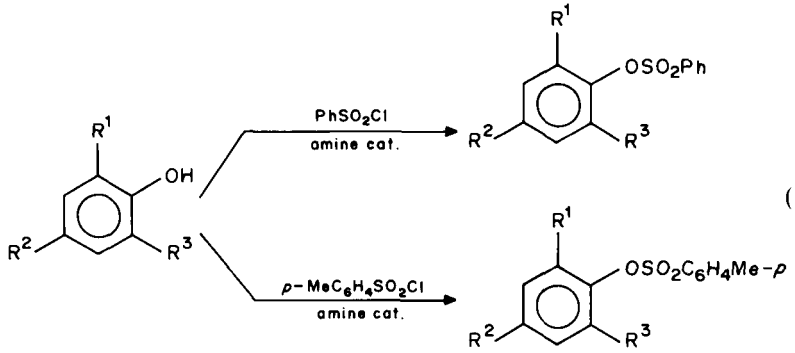
$$EtCHCH_2C{\equiv}CH + EtCHCH{=}C{=}CH_2 + RCOCl \xrightarrow{\text{r.t.}}$$
$$\quad | \qquad\qquad\quad |$$
$$OSn(n\text{-}Bu)_2Cl \qquad OSn(n\text{-}Bu)_2Cl$$
$$(92{:}8)$$
$$EtCHCH_2C{\equiv}CH + EtCHCH{=}C{=}CH_2 \quad (1009)$$
$$\quad | \qquad\qquad\quad |$$
$$OCOR \qquad\qquad OCOR$$
$$(92{:}8)$$

R = Me, $ClCH_2$, Et, *n*-Pr, *t*-Bu, (*E*)-MeCH=CH

Use of an acyl chloride to prepare a thiol ester[2048] involves the reaction of cyclohexanecarboxylic acid chloride with thallium(I) 2-methylpropane-2-thiolate to produce[2048] *S*-(*t*-butyl) cyclohexylmethanethiolate (equation 1010).

$$c\text{-HexCOCl} + \text{TlSCMe}_3 \xrightarrow[\text{stir, 2 h}]{\text{ether, r.t.}} \underset{91\%}{\text{c-HexCOSBu-t}} \qquad (1010)$$

Reaction[2049] of phenyl or *p*-tolyl sulfonyl chloride with phenols in the presence of an amine catalyst affords arenesulfonates (equation 1011). Similar reactions have also been reported[2049] with α- and β-naphthols (equation 1012) using the same reagents and amine catalysts.

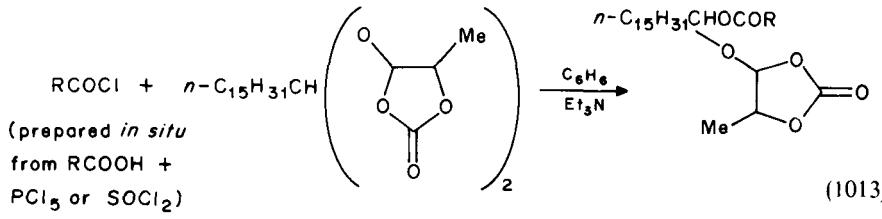


(1011)

Amine Catalyst = Dabco (triethylenediamine), Et_3N or pyridine.

$$\alpha\text{- or } \beta\text{-NaphOH} \xrightarrow[\text{amine cat.}]{\text{PhSO}_2\text{Cl}} \alpha\text{- or } \beta\text{-NaphOSO}_2\text{Ph}$$
$$\alpha\text{- or } \beta\text{-NaphOH} \xrightarrow[\text{amine cat.}]{p\text{-MeC}_6\text{H}_4\text{SO}_2\text{Cl}} \alpha\text{- or } \beta\text{-NaphOSO}_2\text{Tol-}p \qquad (1012)$$

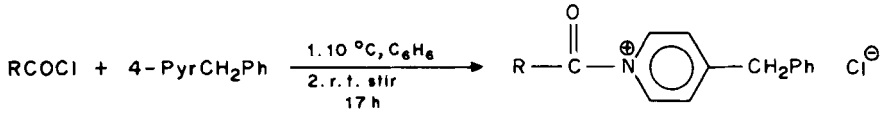
Treatment[2050] of 1,1-di(2-oxo-1,3-dioxalan-4-ylmethyl)hexadecane with acyl chlorides prepared *in situ* from a carboxylic acid and either phosphorus pentachloride or thionyl chloride, affords 1,*O*-(1-acyloxyalkyl)glycero-2,3-carbonates (equation 1013).



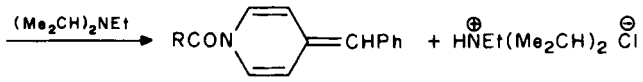
(1013)

R = H, Me, $ClCH_2$, Ph, Me_2CH
% Yield = 73.5 to 96.5

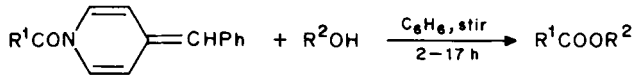
A rather interesting reagent, which may be used to prepare esters by reaction[2051] with alcohols or phenols, is 1-acyl-4-benzylidene-1,4-dihydropyridine. Since this reagent is prepared[2051] by the reaction of acyl chlorides with 4-benzylpyridine (equation 1014) it is presented in this section on ester formation (equation 1015).



(1014)



R =	Ph	*p*-Tol	*p*-An	Me	PhCH=CH
Yield (%) =	85	85	82	65	68



(1015)

R^1 =	Ph	Ph	Me	Me	PhCH=CH	PhCH=CH
R^2 =	Me	Ph	Me	Ph	Me	Ph
Yield (%) =	84	97	63[a]	72	77	79

[a]Required reflux at 70 °C.

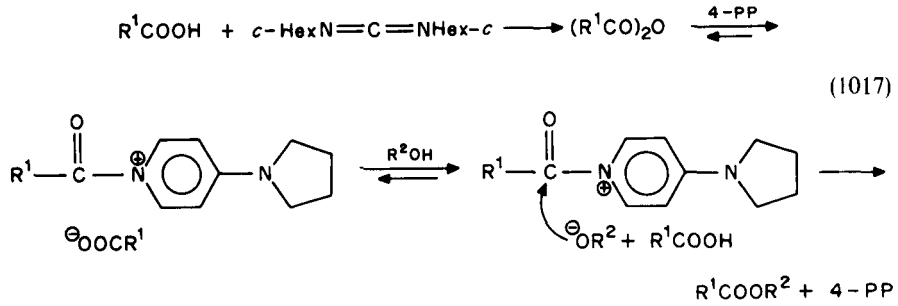
*4. *Alcoholysis of anhydrides*

The ester preparations discussed in this section involve the use of acid anhydrides as acylating agents in reaction with alcohols or phenols. Most of these involve the use of performed acid anhydride substrates, but a few involve the intermediate formation of an acid anhydride, which then reacts further to produce an ester.

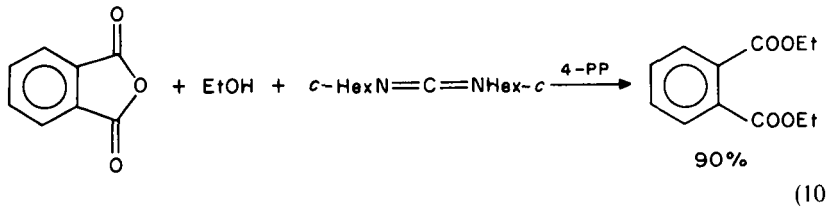
One example[2052] of this latter type of reaction is the one-pot room-temperature esterification of carboxylic acids using alcohols in the presence of *N,N*-dicyclohexylcarbodiimide and 4-pyrrolidinopyridine (4-PP) in ether or dichloromethane at room temperature (equation 1016). The mechanism of this reaction involves the dicyclohexylcarbodiimide effected conversion of the acid to an anhydride, which then forms an arylpyridinium species with the 4-pyrrolidinopyridine catalyst (equation 1017). This species then equilibrates with the alcohol to produce an ion pair. Nucleophilic attack by the alkoxy ion on the acyl group of the ion pair generates the ester and regenerates the catalyst. The acid is recycled by the dicyclohexylcarbodiimide while the catalyst is reused. As can be seen from the examples reported, this procedure may be used to form the *t*-butyl esters of N-protected amino acids. This procedure may also be used to produce diesters from preformed cyclic anhydrides as illustrated in equation 1018.

$$R^1COOH + R^2OH + c\text{-}HexN{=}C{=}NHex\text{-}c \xrightarrow{4\text{-}PP} R^1COOR^2 \quad (1016)$$

R^1	R^2	Rx time (h)	Yield (%)
Ph	Et	0.5	90
Ph	Ph	6	94
Me	*t*-Bu	3	90
p-$BrC_6H_4CH_2$	Et	12	96
Ph_2CH	Et	12	96
2,4,6-$Me_3C_6H_2$	*p*-$O_2NC_6H_4$	12	90
Me_2CH	*t*-Bu	24	65
PhCONHCHMe	$PhCH_2$	2	80
$PhCH_2OCONHCHMe$	*o*-$O_2NC_6H_4CH_2$	2	78
$PhCH_2OCONHCHCH_2Ph$	*o*-$O_2NC_6H_4$	1	71



(1017)

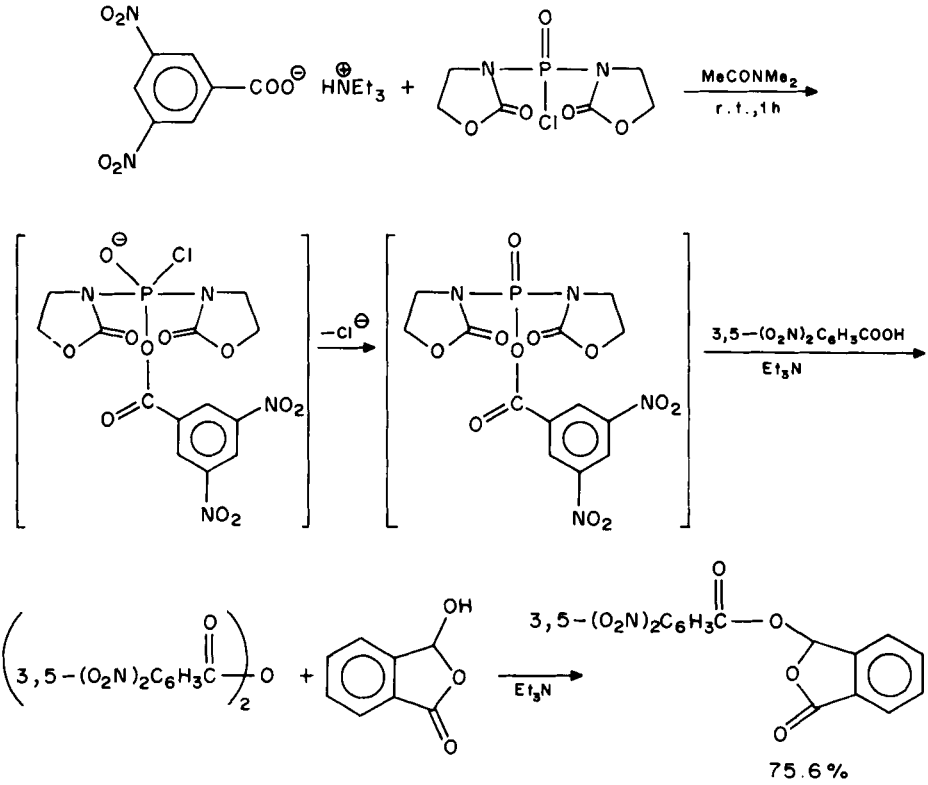


(1018)

The use of phosphorus compounds as coupling agents in esterification reactions has received considerable attention, and these reports all have a similar mechanism in common, which involves the initial formation of a mixed anhydride formed from the carboxylic acid, acid salt or anhydride and the phosphorus compound, which then reacts with an alcohol or phenol to produce the ester. For example, reaction of phosphoryl chloride with benzoic anhydride produces[2053] the mixed carboxylic acid–dichlorophosphoric acid anhydride, which then reacts with *t*-butyl alcohol at 0 °C to form *t*-butyl benzoate (equation 1019).

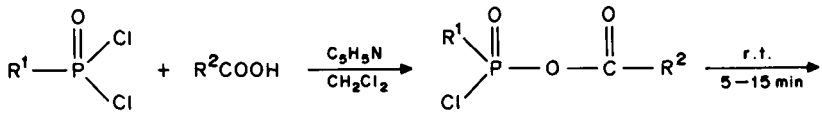
$$(PhCO)_2O + (Cl_2P)_2O \xrightarrow[\substack{PhCOOBu\text{-}t \\ 68\%}]{8h,\ 95^\circ C} PhCOOPCl_2 \xrightarrow[0\ C,\ 3h]{t\text{-}BuOH} \qquad (1019)$$

A slight variation of this mechanism is seen to occur when *N,N*-bis(2-oxo-3-oxazolidinyl)phosphordiamic chloride is used as the coupling agent. Indeed, when this reagent is allowed to react with a carboxylic acid salt a mixed anhydride is initially formed[2019,2054]; however, upon treatment with a base, this intermediate disproportionates to produce the symmetrical carboxylic acid anhydride which then reacts with an alcohol to produce an ester (equation 1020).

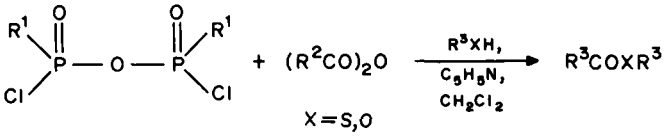


(1020)

Similarly, reaction of phosphorus oxychloride[2055] ($R^1 = Cl$) or phenyldichlorophosphate[2055,2056] ($R^1 = PhO$) with carboxylic acids in the presence of pyridine produces the respective mixed phosphoric acid anhydride, which disproportionates affording the corresponding symmetrical carboxylic acid anhydride. Treatment of the anhydride with alcohols or thiols produces the corresponding ester or thiol ester (equation 1021 and Table 95). This procedure is applicable to acid or base sensitive compounds, a broad range of

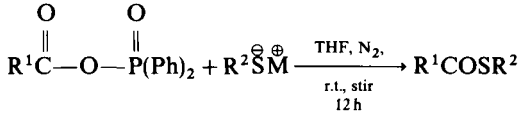


(1021)



structural thiols from primary to tertiary, as well as phenyl and benzyl thiols, and is independent of the steric requirements of the alcohols or thiols.

Thiol esters have also been prepared[2057] by the treatment of mixed diphenylphosphoric acid anhydrides with sodium or potassium salts of thiols (equation 1022). As can be seen from the example presented below, the potassium salts gave consistently higher yields of the esters than did their sodium counterparts.

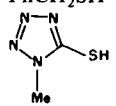
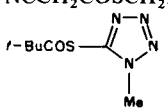
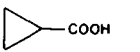
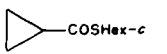
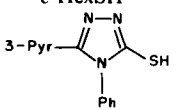
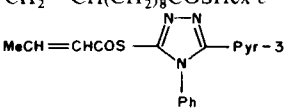
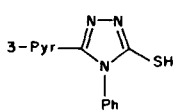
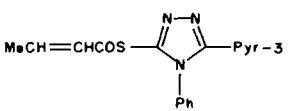


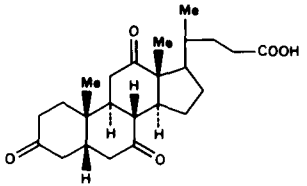
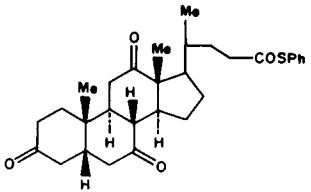
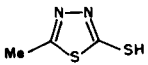
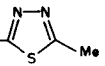
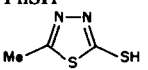
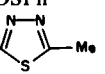
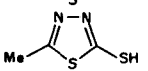
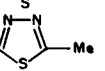
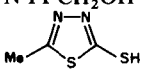
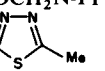
(1022)

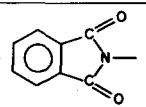
R^1	$R^2\overset{\ominus}{S}\overset{\oplus}{M}$	Product	Yield (%)
c-Hex	*t*-BuSK	*c*-HexCOSBu-*t*	75
c-Hex	*t*-BuSNa	*c*-HexCOSBu-*t*	70
c-Hex	$MeCH_2CH(Me)SK$	*c*-HexCOSCH(Me)CH_2Me	83
c-Hex	$MeCH_2CH(Me)SNa$	*c*-HexCOSCH(Me)CH_2Me	82
c-Hex	*c*-HexSK	*c*-HexCOSHex-*c*	83
c-Hex	*c*-HexSNa	*c*-HexCOSHex-*c*	77
n-Pen	*t*-BuSK	*n*-PenCOSBu-*t*	73
n-Pen	$MeCH_2CH(Me)SK$	*n*-PenCOSCH(Me)CH_2Me	85
Ph	*t*-BuSK	PhCOSBu-*t*	75
Ph	$MeCH_2CH(Me)SK$	PhCOSCH(Me)CH_2Me	75

Nitrogen compounds used as coupling agents in esterification reaction with acid anhydrides also have representation in the recent literature. These reactions fall into the same two mechanistic categories that were discussed for phosphorus compounds, i.e. initial formation of a mixed anhydride or direct esterification of a performed anhydride. Thus, reaction of 2-pyridyl chloroformate with a carboxylic acid in the presence of triethylamine produces[2058] the mixed anhydride and a small amount of the desired ester. Treatment of the mixed anhydride with 4-(dimethylamino) pyridine produces the major

TABLE 95. Ester preparation using mixed phosphoric acid anhydrides[a]

R^2COOH	R^3XH	Reagent and solvent	Time (h)	Product	Yield (%)	Reference
n-$C_{15}H_{31}COOH$	PhSH	$PhOPOCl_2$, DME	16	n-$C_{15}H_{31}COSPh$	99	2056
MeCH(Cl)COOH	t-BuSH	$PhOPOCl_2$, DME	16	MeCH(Cl)COSBu-t	82	2056
n-HexCH(OH)$(CH_2)_{10}$COOH	PhSH	$PhOPOCl_2$, DME	16	n-HexCH(OH)$(CH_2)_{10}$COSPh	78	2056
$EtOCH_2COOH$	$PhCH_2SH$	$PhOPOCl_2$, DME	16	$EtOCH_2COSCH_2Ph$	100	2056
$PhOCH_2COOH$	$PhCH_2SH$	$PhOPOCl_2$, DME	16	$PhOCH_2COSCH_2Ph$	99	2056
$PhOCH_2COOH$	t-BuSH	$PhOPOCl_2$, DME	16	$PhOCH_2COSBu$-t	98	2056
PhOCH(Me)COOH	n-BuSH	$PhOPOCl_2$, DME	16	PhOCH(Me)COSBu-n	99	2056
PhOCH(Me)COOH	t-BuSH	$PhOPOCl_2$, DME	16	PhOCH(Me)COSBu-t	98	2056
$NCCH_2COOH$	t-BuSH	$PhOPOCl_2$, DME	16	$NCCH_2COSBu$-t	65	2056
$NCCH_2COOH$	$PhCH_2SH$	$PhOPOCl_2$, DME	16	$NCCH_2COSCH_2Ph$	89	2056
t-BuCOOH		Cl_3PO, CH_2Cl_2	20		60	2055
t-BuCOOH	c-HexSH	$PhOPOCl_2$, DME	16	t-BuCOSHex-c	88	2056
	c-HexSH	$PhOPOCl_2$, DME	16		97	2056
c-HexCOOH	$PhCH_2SH$	$PhOPOCl_2$, DME	16	c-HexCOSCH$_2$Ph	92	2056
c-HexCOOH	PhSH	$PhOPOCl_2$, DME	16	c-HexCOSPh	100	2056
CH_2=CH$(CH_2)_8$COOH	c-HexSH	$PhOPOCl_2$, DME	16	CH_2=CH$(CH_2)_8$COSHex-c	88	2056
MeCH=CHCOOH		Cl_3PO, CH_2Cl_2	20		60	2055
MeCH=CHCOOH		$PhOPOCl_2$, CH_2Cl_2	24		60	2055
PhCH=CHCOOH	PhSH	Cl_3PO, CH_2Cl_2	20	PhCH=CHCOSPh	93	2055
PhCH=CHCOOH	PhSH	$PhOPOCl_2$, DMF	14	PhCH=CHCOSPh	89	2055
PhCH=CHCH=CHCOOH (*trans, trans*)	n-BuSH	$PhOPOCl_2$, DME	16	PhCH=CHCH=CHCOSBu-n (*trans, trans*)	100	2056

	PhSH	$PhOPOCl_2$, DME	16		95	2056
N-PI-CH_2COOH	*t*-BuOH	Cl_3PO, CH_2Cl_2	24	N-PI-CH_2COOBu-*t*	83	2055
N-PI-CH_2COOH	*t*-BuOH	Cl_3PO, DMF	2	M-PI-CH_2COOBu-*t*	74	2055
N-PI-CH_2COOH	*t*-BuOH	PhOPOCl, CH_2Cl_2	3	N-PI-CH_2COOBu-*t*	80	2055
N-PI-CH_2COOH	N-PI-CH_2OH	Cl_3PO, CH_2Cl_2	3	N-PI-CH_2COOCH_2N-PI	83	2055
N-PI-CH_2COOH	$PhCH_2OH$	Cl_3PO, CH_2Cl_2	10	N-PI-CH_2COOCH_2Ph	80	2055
N-PI-CH_2COOH	$PhCH_2OH$	$PhOPOCl_2$, DMF	1	N-PI-CH_2COOCH_2Ph	95	2055
N-PI-CH_2COOH	PhSH	$PhOPOCl_2$, DMF	24	N-PI-CH_2COSPh	70	2055
N-PI-CH_2COOH	*n*-PrSH	$PhOPOCl_2$, DMF	14	N-PI-CH_2COSPr-*n*	73	2055
N-PI-CH_2COOH		$PhOPOCl_2$, DMF	22	N-PI-CH_2COS- 	83	2055
N-PI-CH(Me)$COOH$	*t*-BuOH	$PhOPOCl_2$, DMF	3	N-PI-CH(Me)$COOBu$-*t*	82	2055
N-PI-CH(Me)$COOH$	*t*-BuOH	Cl_3PO, DMF	2	N-PI-CH(Me)$COOBu$-*t*	65	2055
o-TolCOOH	PhSH	$PhOPOCl_2$, DME	16	*o*-TolCOSPh	98	2056
p-MeCONHC_6H_4COOH	PhSH	$PhOPOCl_2$, DME	16	*p*-MeCONHC_6H_4COSPh	96	2056
2,6-$(MeO)_2C_6H_3COOH$		Cl_3PO, CH_2Cl_2	16	2,6-$(MeO)_2C_6H_3COS$- 	93	2055
2,6-$(MeO)_2C_6H_3COOH$		$PhOPOCl_2$, DMF	20	2,6-$(MeO)_2C_6H_3COS$- 	90	2055
2,6-$Cl_2C_6H_3COOH$	PhSH	$PhOPOCl_2$, CH_2Cl_2	24	2,6-$Cl_2C_6H_3COSPh$	92	2055
3,5-$(O_2N)_2C_6H_3COOH$	*t*-BuOH	$PhOPOCl_2$, DMF	3	3,5-$(O_2N)_2C_6H_3COOBu$-*t*	85	2055
3,5-$(O_2N)_2C_6H_3COOH$	*t*-BuOH	Cl_3PO, DMF	3	3,5-$(O_2N)_2C_6H_3$	71	2055
3,5-$(O_2N)_2C_6H_3COOH$	*c*-HexOH	Cl_3PO, CH_2Cl_2	24	3,5-$(O_2N)_2C_6H_3COOCH_2$N-PI	70	2055
3,5-$(O_2N)_2C_6H_3COOH$	Me_2CHOH	Cl_3PO, DMF	3	3,5-$(O_2N)_2C_6H_3COOCHMe_2$	80	2055
3,5-$(O_2N)_2C_6H_3COOH$	N-PI-CH_2OH	Cl_3PO, CH_2Cl_2	24	3,5-$(O_2N)_2C_6H_3COOCH_2$N-PI	89	2055
3,5-$(O_2N)_2C_6H_3COOH$		Cl_3PO, CH_2Cl_2	16	3,5-$(O_2N)_2C_6H_3COS$- 	78	2055
3,5-$(O_2N)_2C_6H_3COOH$	*n*-PrSH	$PhOPOCl_2$, DMF	24	3,5-$(O_2N)_2C_6H_3COSPr$-*n*	89	2055

[a] N-PI = *N*-Phthalimido ≡ 

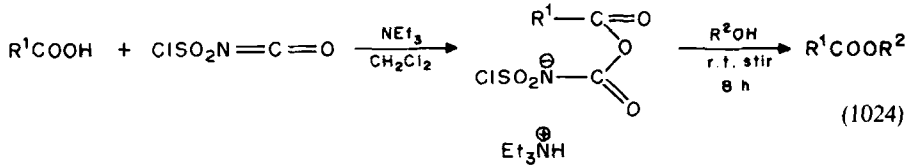
yield of ester (equation 1023) reported below.

$$2\text{-PyrOH} + COCl_2 \xrightarrow{Et_3N} 2\text{-PyrOCOCl} + RCOOH \xrightarrow[\substack{CH_2Cl_2\\0\,^\circ C,\ 30\,min}]{Et_3N}$$
$$2\text{-PyrOC(O)OC(O)R} + 2\text{-PyrOCOR} \xrightarrow{4\text{-PyrNMe}_2} 2\text{-PyrOCOR} \qquad (1023)$$

R =	Ph	*n*-Pr	*i*-Pr	*t*-Bu	2,4,6-$Me_3C_6H_2$	$PhCOCH_2CH_2$
% Yield =	92	93	87	83	92	80

R =	$MeOOC(CH_2)_4$	$Br(CH_2)_5$	$PhCH{=}CH$
% Yield =	85	89	86

Initial formation of a mixed anhydride, which is then allowed to react with an alcohol to produce an ester, also occurs[2059] when carboxylic acids react with chlorosulfonyl isocyanate in triethylamine (equation 1024).



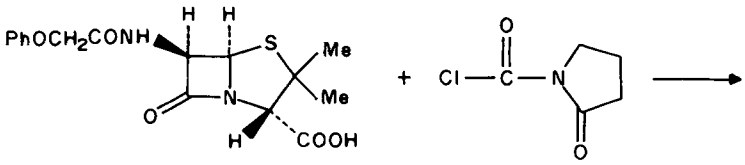
(1024)

R^1	R^2	Yield (%)
n-$C_{11}H_{23}$	Et	80
$PhCH_2$	Et	78
$PhCH_2$	Ph	72
$MeCH{=}CH$	Me	70
$PhCH{=}CH$	Ph	68
Ph	Me	88
Ph	Et	83
Ph	$PhCH_2$	77
Ph	Ph	75

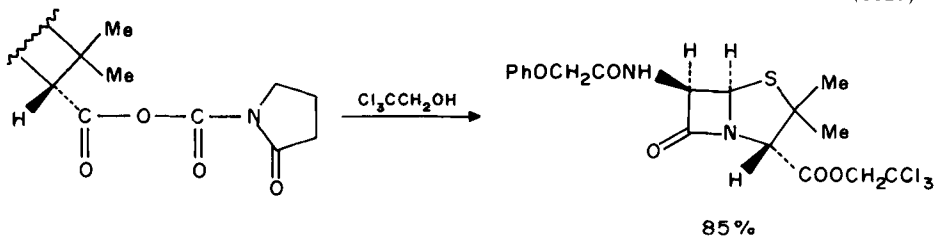
Similarly, reaction of 6-phenoxyacetamidopenicillanic acid (Penicillin G) with *N*-chlorocarbonyl-2-pyrrolidinone[2059] (equation 1025) or ethoxycarbonyl chloride[2060] (equation 1026) produces the corresponding mixed anhydride which, upon alcoholysis, affords the appropriate esters.

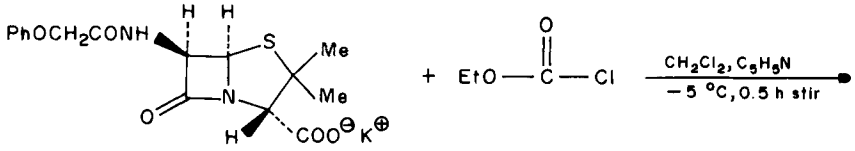
The nature of the product obtained when cyclic anhydrides undergo esterification is directly dependent upon the structure of the substrate with which the anhydrides reacts. For instance, reaction of phthalic anhydride with 1,2,3-trichloropropene-1 in the presence of benzyl trimethylammonium chloride and sodium carbonate produces[2061] the symmetrical bis(2,3-dichloroalkyl)phthalate ester (equation 1027).

Symmetrical diesters are also produced[2062] when phthalic (equation 1028), maleic (equation 1029) or succinic (equation 1030) anhydrides react with methanol and methyl *t*-butyl ether in the presence of the cation exchange catalyst Ostion KS in its acid form.

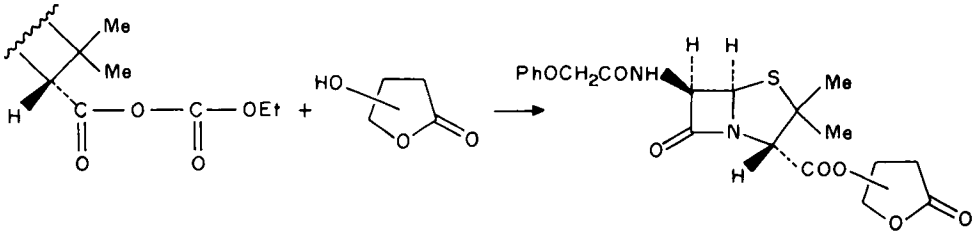


(1025)

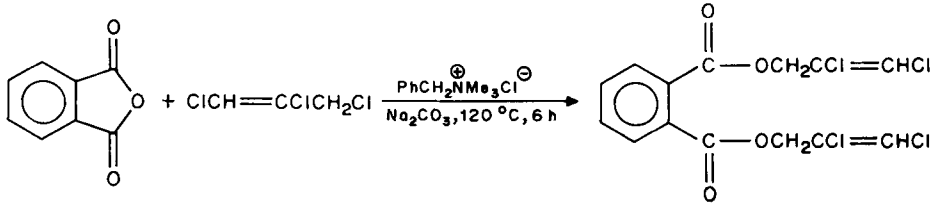




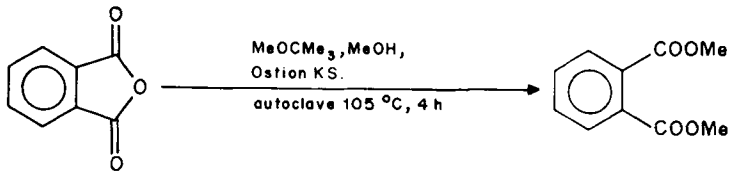
(1026)



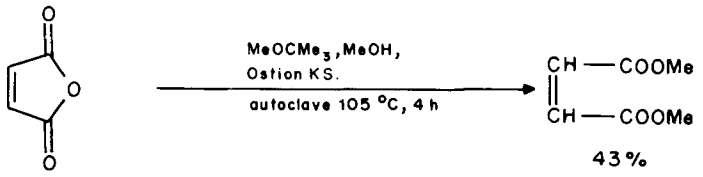
(With 3-hydroxybutyrolactone—65% yield; with 5-hydroxybutyrolactone—59% yield).



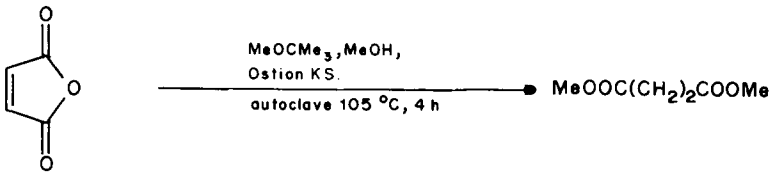
(1027)



(1028)

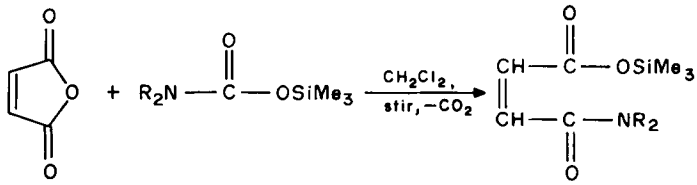


(1029)



(1030)

An example of the formation of an unsymmetrical product resulting from the reaction of a cyclic anhydride is illustrated by the reaction[2063] of maleic anhydride with trimethylsilyl *N*-alkylcarbonate (equation 1031) where a monoester monoamide product is formed.



(1031)

R	Temp. (°C)	Time (min)	Yield (%)
Me	25	30	83
Et	25	60	91
n-Pr	80	60	93
n-Bu	80	60	87

*5. *Alcoholysis of ketenes*

In this section the reactions of ketenes with alcohols or phenols to afford esters are presented. The reports discussed are those which involve stable ketene substrates or ketenes proposed as nonisolatable intermediates in a reaction mechanism.

One example of the former type of reaction is the preparation[2064] of optically active α-substituted esters by condensation of the nonsymmetrical ketene *p*-chlorophenyl isopro-

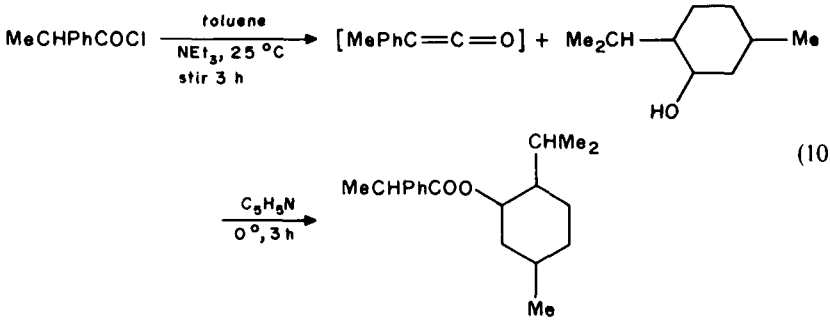
pyl ketene with the optically active 1-phenylethanol in the presence of an optically active amino acid or peptide (equation 1032).

$$p\text{-}ClC_6H_4C(i\text{-}Pr)=C=O + HOCHMePh \xrightarrow[\text{toluene}]{\text{catalyst}} p\text{-}ClC_6H_4CH(i\text{-}Pr)COOCHMePh \quad (1032)$$

diastereisomeric ratio
41:59

Catalyst—cyclo(L-Phenylalanine-L-Histidine)

An example of the latter approach to the preparation of esters involves the *in situ* preparation of methyl phenyl ketene, from reaction of 1-phenylpropionyl chloride with triethylamine, followed by condensation[2065] with 1-menthol (equation 1033).



(1033)

*6. *Alcoholysis of nitriles and amides*

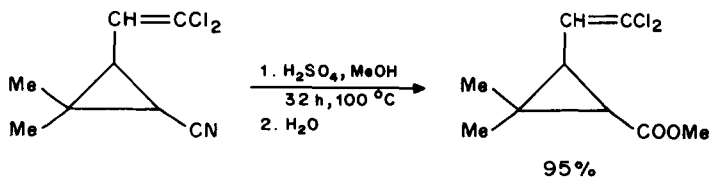
Recent reports of the alcoholysis of nitriles to produce esters have included reaction of alcohols with a variety of structurally different nitriles. As an example of alcoholysis of a simple nitrile is the report[2066] of the methanolysis of propionitrile in the presence of an iridium catalyst complexed with hydroxo and tertiary phosphine moieties (equation 1034).

$$EtCN + MeOH \xrightarrow[175\,°C,\ 4\,h]{Ir(OH)(CO)(PPh_3)_2} EtCOOMe \quad (1034)$$

67%

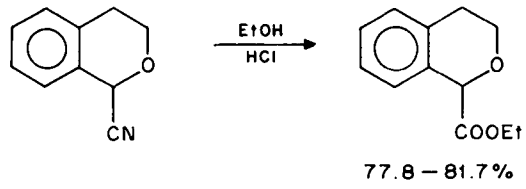
Cycloalkyl nitriles which have been converted to esters upon treatment with alcohols include cyclopropyl nitriles[2067] (equation 1035) and isochroman-1-nitrile[2068] (equation 1036).

One recent example of a cycloalkenyl nitrile which has been converted to an ester by



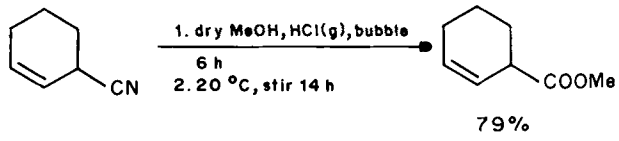
(1035)

95%

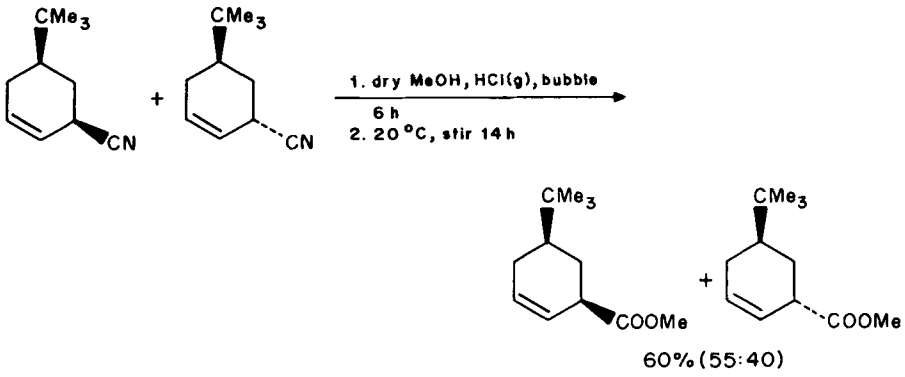


(1036)

treatment[2069] with an alcohol is cyclohex-2-enyl nitrile (equation 1037) and a mixture of its 5-*t*-butyl substituted *cis* and *trans* analogues[2069] (equation 1038). The ester products obtained from the latter reaction were separated by preparative glc.

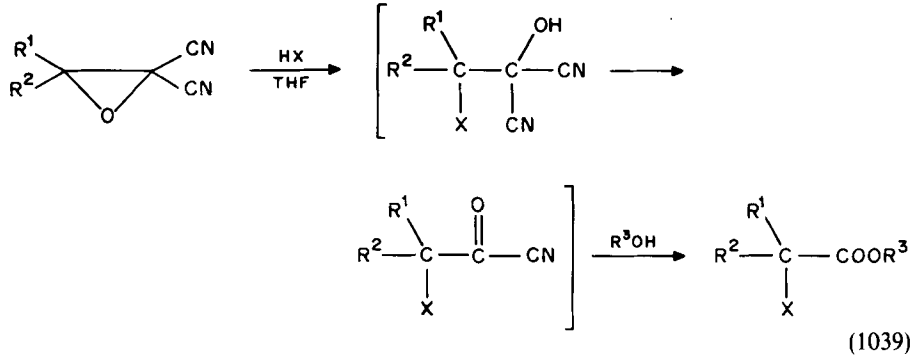


(1037)

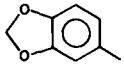


(1038)

By using a one-pot reaction of *gem*-dicyano epoxides with a hydrohalic acid in alcohol media, α-halo esters have been prepared[1549,2070] in good yields (equation 1039).



(1039)

R^1	R^2	R^3	X	Yield (%)
Ph	H	Me	Br	90
p-ClC_6H_4	H	Me	Br	85
p-ClC_6H_4	H	Et	Br	88
p-ClC_6H_4	H	Et	Cl	90
p-ClC_6H_4	H	*i*-Pr	Br	85
p-$O_2NC_6H_4$	H	Et	Br	95
p-$O_2NC_6H_4$	H	Et	Cl	90
m-$O_2NC_6H_4$	H	*i*-Pr	Br	85
p-Tol	H	Et	Br	86
p-Tol	H	Me	F	80
	H	Et	Cl	85
Ph	Me	Et	Cl	90
m-BrC_6H_4	Me	Et	Cl	70
Ph	Me	Et	H	90[a]
m-BrC_6H_4	Me	Et	H	70[a]
$PhCH_2$	Me	Et	Br	65
Et	H	Et	Br	70
Me	COOEt	Et	Cl	80
Ph	COOEt	Et	Cl	80
Me	COOEt	Et	H	80[a]
Ph	COOEt	Et	H	80[a]

[a] Prepared by reduction of the α-halo ester using zinc in acetic anhydride.

Amides may also be used as substrates in alcoholysis reactions to prepare esters, as illustrated by the reaction[2071] of 2-hydroxy-2-methylpropionamide with methanol in an autoclave at 200 °C catalyzed by lithium hydroxide (equation 1040).

$$Me_2C(OH)CONH_2 + MeOH \xrightarrow[200\,^\circ C,\ LiOH]{\text{autoclave}} \underset{11\%}{Me_2C(OH)COOMe} \qquad (1040)$$

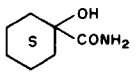
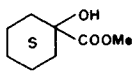
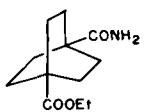
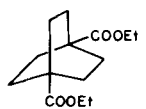
Another amide to ester conversion performed in an autoclave is the transformation[2072] of acetamide to methyl acetate. This reaction requires the use of methyl formate and carbon monoxide as reagents and iron acetylacetonate and triphenylphosphine as catalysts (equation 1041).

$$MeCONH_2 + HCOOMe + CO(55\,kg/cm^2) \xrightarrow[\substack{\text{iron acetylacetonate}\\ Ph_3P,\ 200\,^\circ C,\ 3.5\,h}]{\text{autoclave}} MeCOOMe \qquad (1041)$$

An example of a convenient laboratory conversion of amides or hydrazines to esters is illustrated by the reaction[2073] of either substrate above with an acidic resin (Amberlyst 15, XN-1010 or 120) in the presence of methanol or ethanol (equation 1042 and Table 96). Although this reaction does produce clean, easily isolatable products and is specific for unsubstituted carboxamides, N-substitution completely prevents alcoholysis as can be seen from several entries in Table 96.

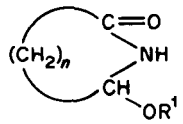
$$\left.\begin{matrix} R^1CONH_2 \\ \text{or} \\ R^1CONHNH_2 \end{matrix}\right\} \xrightarrow[\substack{\text{MeOH or EtOH}\\ \text{reflux}}]{\text{Amberlyst cat.}} R^1COOR^2 \qquad (1042)$$

TABLE 96. Ester preparation from amides and hydrazines using Amberlyst[2074]

Substrate	Resin Amberlyst	Solvent	Temp. (°C)	Time (h)	Product	Yield (%)
$PhCONH_2$	15	MeOH	60	96	PhCOOMe	70
$PhCH{=}CHCONH_2$	15	MeOH	60	144	$PhCH{=}CHCOOMe$	62
D,L-$PhCONHCHMeCONH_2$	15	MeOH	60	24	$PhCONHCHMeCOOMe$	89
L-$PhtNCH(CH_2Ph)CONH_2$	15	MeOH	60	144	$PhtNCH(CH_2Ph)COOMe$	87[a]
L-$PhtNCH(CH_2Ph)CONH_2$	XN-1010	MeOH	60	18	$PhtNCH(CH_2Ph)COOMe$	86[a]
L-$PhtNCH(CH_2Ph)CONH_2$	120	MeOH	60	24	$PhtNCH(CH_2Ph)COOMe$	91[a]
L-$PhtNCH(CH_2Ph)CONH_2$	15	EtOH	60	144	$PhtNCH(CH_2Ph)COOEt$	84[a]
$CH_2{=}CH(CH_2)_8CONH_2$	15	MeOH	60	48	$CH_2{=}CH(CH_2)_8COOMe$	94
$CH_2(CONH_2)_2$	15	MeOH	60	24	$CH_2(COOMe)_2$	63
$N{\equiv}CCH_2CONH_2$	15	MeOH	60	18	$N{\equiv}CCH_2COOMe$	85
$H_2NCOCH_2CH(NH_2)COOH{\cdot}H_2O$ (DL)	15	MeOH	60	96	$MeOOCCH_2CH(NH_2)COOMe$	77
	15	MeOH	60	48		63
	XN-1010	EtOH	75	120		66
$PhCONMe_2$	15	MeOH	60	168	No reaction	
$PhCONMe_2$	XN-1010	MeOH	60	168	No reaction	
$PhCONMe_2$	120	MeOH	60	168	No reaction	
$PhCONHNH_2$	15	MeOH	60	24	PhCOOMe	68
$PhCONHCH_2CONHNH_2$	15	MeOH	60	20	$PhCONHCH_2COOMe$	78
D,L-CBZ-Val-Tyr-$NHNH_2$	15	MeOH	60	2	CBZ-Val-TyrOMe	62

[a] Pht = phthaloyl.

Preparation of esters is reported[2074] to occur during acidic alcoholysis of ω-alkoxylactams producing esters of ω,ω-dialkoxycarboxylic acids (equation 1043).



$$\xrightarrow[2-12\ h\ reflux]{R^1OH,\ HCl} (R^1O)_2CH(CH_2)_nCOOR^1 \qquad (1043)$$

R^1	n	Product	Yield (%)
Et	2	$(EtO)_2CH(CH_2)_2COOEt$	52
Me	3	$(MeO)_2CH(CH_2)_3COOMe$	60
n-Bu	3	$(n\text{-}BuO)_2CH(CH_2)_3COOBu\text{-}n$	50
Me	4	$(MeO)_2CH(CH_2)_4COOMe$	69
Me	10	$(MeO)_2CH(CH_2)_{10}COOMe$	51

*7. *Transesterification*

The transesterification reactions reported in the recent literature have been performed on a variety of substrates using various conditions and catalysts. Among the simple acid and/or base catalyzed transesterification reactions reported are: the formation of methyl acetate from 1,4-butanediol diacetate using methanol in the presence[2075] of acid or base (equation 1044), or from 2-butene-1,4-diol diacetate using methanol in the presence[2075] of base (equation 1044); conversion of the methyl ester of pregnadienonaphthaleno-21-carboxylic acid (PDN-21-COOMe) into its corresponding isopropyl ester by reaction[2076] with isopropyl alcohol in acid (equation 1045); and the conversion of alkyl vinyl monoesters (equation 1046) and diesters (equations 1047 and 1048) into their corresponding aromatic analogues by reaction[2077] with phenol in the presence of a base.

$$\left.\begin{array}{l}(CH_2CH_2OOCMe)_2 + MeOH \xrightarrow[NaOMe]{H_2SO_4\ or} \\ (=CHCH_2OOCMe)_2 + MeOH \xrightarrow{NaOMe}\end{array}\right\} \longrightarrow MeOOCMe \qquad (1044)$$

$$PDN\text{-}21\text{-}COOMe + i\text{-}PrOH \xrightarrow{H^+} PDN\text{-}21\text{-}COOPr\text{-}i \qquad (1045)$$

$$R^1COOCH{=}CH_2 + R^2OH \xrightarrow[95\,^\circ C,\ 3\,h]{base} R^1COOR^2 \qquad (1046)$$

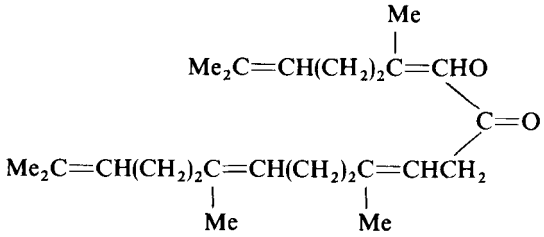
R^1	R^2	Base	Yield (%)
Me	Ph	NaOPh, Na, KOH or KOPh	81–87
Me	Ph	LiOPh	70
n-Pr	Ph	NaOPh	—
Me	RC_6H_4 R = *p*-Cl; *p*-Me; *o*-Cl; *p*-Me_3C; *p*-MeO_2C; *p*-O_2N	NaOPh	—

$$MeCOOCH{=}CH_2 + p\text{-}HOC_6H_4OH \xrightarrow[95\,^\circ C,\ 3\,h]{NaOPh} p\text{-}MeCOOC_6H_4OOCMe \qquad (1047)$$

$$H_2C{=}CHOOC(CH_2)_4COOCH{=}CH_2 + PhOH \xrightarrow[95\,^\circ C,\ 3\,h]{NaOPh} PhOOC(CH_2)_4COOPh \qquad (1048)$$

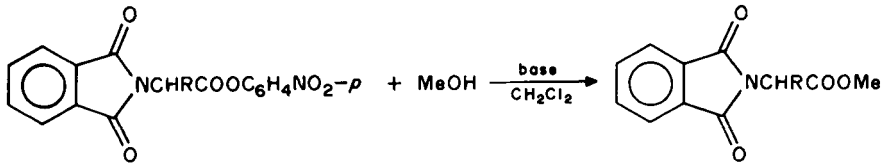
Base-catalyzed transesterification has also been reported[2078] when a halide is used instead of an alcohol. Thus, treatment of geranyl acetate with farnesyl bromide in the presence of lithium *n*-butoxide, pyrrolidine and copper iodide produces (equation 1049) a 93% yield of geranyl farnesylacetate. Similarly prepared[2078] were genanyl geranylgeranylacetate, farnesyl geranylgeranylacetate, ethyl geranylgeranylacetate and phytyl geranylgeranylacetate.

$$Me_2C{=}CHCH_2CH_2\underset{\displaystyle Me}{\underset{|}{C}}{=}CHCH_2O{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}Me \xrightarrow[\text{pyrrolidine, CuI, } N_2,\ -78\,^\circ C]{\text{1. LiOBu-}n\text{, hexane, THF}} \xrightarrow[30\,min]{\text{2. THF, farnesyl bromide,}} \qquad (1049)$$



93%

A significant number of metal-catalyzed transesterification reactions have also been reported. Inorganic metal salts as well as organometallic compounds are all represented as catalysts for ester exchange reactions, and in this section we will present the reports of their use. Reaction of *N*-phthaloylamino acid *p*-nitrophenyl ester with methanol in the presence of cesium fluoride produces[2079] the optically pure *N*-phthaloylamino acid methyl ester (equation 1050), which is in drastic contrast to the considerable racemization which was reported[2079] to occur when the same reaction was attempted using triethylamine instead of cesium fluoride.



(1050)

R	Base	% Optical purity
Me	CsF	98
$PhCH_2$	CsF	95
Me	NEt_3	57
$PhCH_2$	NEt_3	79

Ester exchange of carboxylic acids, phosphorus acid and dialkylcarbonoic acid esters have been effected by treatment of the initial esters with alkoxo or phenoxo group containing copper compounds and alcohols or phenols[2080]. One example of this approach is the ethyl for methyl ester exchange in methyl 2-methylpropen-2-oate (equation 1051).

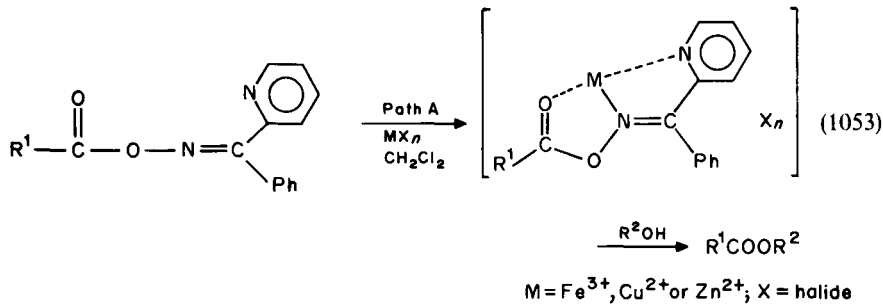
$$H_2C{=}C(Me)COOMe + EtOH \xrightarrow[\text{THF, 50–60 °C}]{\text{PhOCu(PPh}_3)_2} H_2C{=}C(Me)COOEt \quad (1051)$$

Treatment of the same substrate with *n*-butyl alcohol in the presence of zinc acetylacetonate has also been reported[2081] to effect transesterification (equation 1052) in excellent yields.

$$CH_2{=}C(Me)COOMe + n\text{-BuOH} \xrightarrow[\text{reflux, 1.5 h}]{\text{zinc acetylacetonate}} CH_2{=}C(Me)COOBu\text{-}n \quad (1052)$$

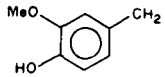
99.2%

A rather interesting metal-catalyzed transesterification reaction has been reported[2082] which involves (*E*)-phenyl 2-pyridyl ketone *O*-acyloximes (PPAOs). Using this substrate two approaches have been used to produce esters. In the first approach, Path A, the PPAOs are allowed to react with metal ions such as Fe^{3+}, Cu^{2+} or Zn^{2+} to complex with and activate the substrate. These resulting complexes are so highly activated by the metal ions that they permit reaction with alcohols to occur which are not possible without the metal ion catalyst. The authors[2082] consider this conversion as a synthetic model reaction of metalloenzymes in which the phenyl 2-pyridyl ketone *O*-acyloximes are activated by the metal ions (equation 1053). As can be seen from the results reported, the most effective catalyst system for the Path A reaction was zinc chloride in a methylene chloride/acetonitrile solvent mixture, which could even be used to produce sterically hindered esters.

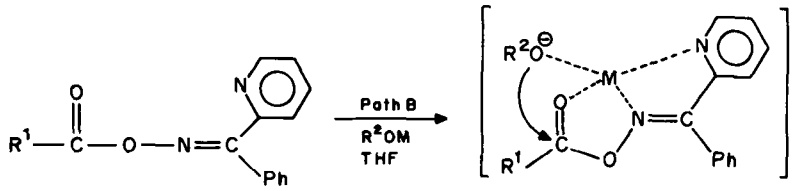


(1053)

R^1	R^2	Metal MX_n	Solvent	Time (h)	Yield (%)
n-$C_{15}H_{31}$	$PhCH_2$	—	CH_2Cl_2	24	0
n-$C_{15}H_{31}$	$PhCH_2$	$FeCl_3$	CH_2Cl_2	18	76
n-$C_{15}H_{31}$	$PhCH_2$	$FeCl_3$	CH_2Cl_2/MeCN	18	73
n-$C_{15}H_{31}$	$PhCH_2$	$CuCl_2$	CH_2Cl_2	5	70
n-$C_{15}H_{31}$	$PhCH_2$	$CuCl_2$	CH_2Cl_2/MeCN	18	90
n-$C_{15}H_{31}$	$PhCH_2$	$ZnCl_2$	CH_2Cl_2/MeCN	18	92
Ph	$PhCH_2$	$ZnCl_2$	CH_2Cl_2/MeCN	18	96

R^1	R^2	Metal MX_n	Solvent	Time (h)	Yield (%)
PhCH=CH (*trans*)	$PhCH_2$	$ZnCl_2$	CH_2Cl_2/MeCN	18	92
t-Bu	$PhCH_2$	$ZnCl_2$	CH_2Cl_2/MeCN	48	69
2-Pyr	$PhCH_2$	$ZnCl_2$	CH_2Cl_2/MeCN	18	76
n-$C_{15}H_{31}$		$ZnCl_2$	CH_2Cl_2/MeCN	24	89

In the second approach, Path B, the PPAOs are allowed to react[2082] with alcoholates to produce the corresponding sterically hindered esters in good to excellent yields. This approach involves capture of the counter cations of the alcoholates by the PPAOs, thus allowing the reactive, free alcoholate anions the opportunity to attack the PPAOs (equation 1054).



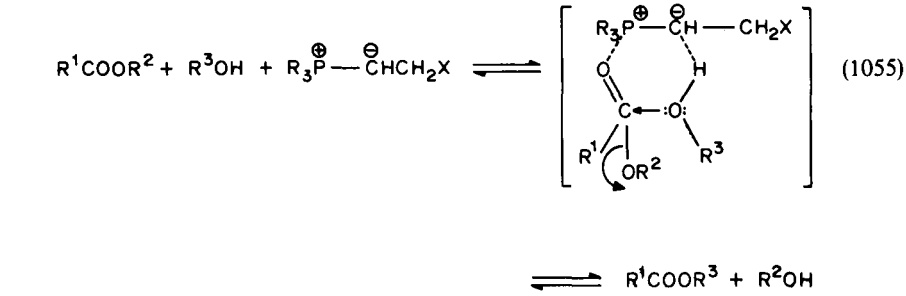
(1054)

$\longrightarrow R^1COOR^2$

$M = Li^+, Na^+ \text{ or } K^+$

R^1	R^2OM	Time (min)	Yield (%)
Ph	$PhCH_2OLi$	< 5	97
Ph	$PhCH_2ONa$	< 5	94
Ph	$PhCH_2OK$	20	98
n-$C_{15}H_{31}$	$PhCH_2ONa$	< 5	96
PhCH=CH (*trans*)	$PhCH_2ONa$	< 5	98
PhCH=CH (*trans*)	*t*-BuOLi	< 5	95
PhCH=CH (*trans*)	*t*-BuOK	25	93
t-Bu	$PhCH_2OLi$	< 5	97
t-Bu	$PhCH_2ONa$	15	97
t-Bu	$PhCH_2OK$	35	90
2-Pyr	$PhCH_2ONa$	< 5	73

Phosphorus ylides have also been reported[2083] to catalyze transesterification reactions and it was found that, in reactions using these catalysts, esters which contained an electron-withdrawing group reacted rapidly with methanol to produce the methyl esters in high yields. It was further observed[2083] that higher esters react rapidly with methanol in the presence of these catalysts to afford the methyl esters quantitatively, but that the reverse reaction, that is the formation of higher esters from methyl esters, proceeded only slowly or not at all. Also, benzyl and *t*-butyl esters did not react when treated with methanol in the presence of phosphorus ylides, and the ylides derived from tri-(*n*-butyl) phosphine had a greater catalytic effect than the ylides derived from triphenylphosphine. The mechanism proposed[2082] for these reactions involves formation of a six-membered intermediate as shown in equation 1055. Results of these transesterifications are reported in Table 97.



(1055)

Among the organometallic reagents reported[2084] to catalyze ester interchange reactions is di(*n*-butyl)tin oxide, which can be used to prepare carboxylic acid esters of secondary and tertiary alcohols from carboxylic acid esters of primary alcohols (equation 1056).

$$R^1COOMe + R^2OH \xrightarrow[\text{autoclave, } N_2,\ 6\,h]{(n\text{-}Bu)_2SnO,\ 120\,^\circ C} R^1COOR^2 \qquad (1056)$$

R^1 =	*n*-C_5H_{11}	*c*-C_6H_{11}	Ph	Ph	*p*-HOC_6H_4
R^2 =	*i*-Pr	*i*-Pr	MeCHEt	*t*-Bu	*i*-Pr
% Yield =	—	—	—	—	72

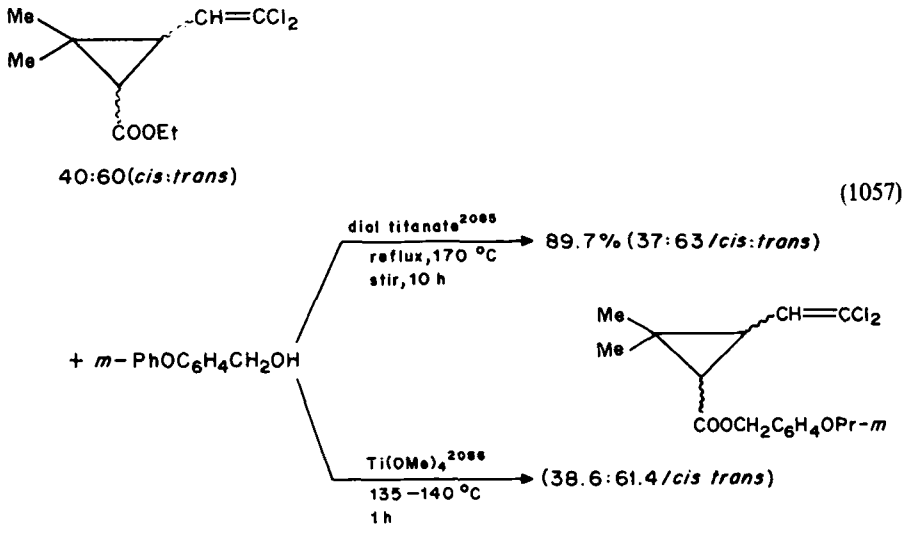
Several examples of the use of titanium organometallic compounds in transesterification reactions have appeared recently. These reports have included the use of a diol titanate catalyst[2085], prepared by treating di-(*i*-propyl)titanate with 1,3-pentanediol in petroleum ether at 40 °C for 2 hours, or the use of tetramethoxytitanate[2086], to effect ester exchange of ethyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate with *m*-phenoxybenzyl alcohol (equation 1057). The resulting *m*-phenoxybenzyl ester products find use as insecticides.

Titanium organometallic catalysts can also be used to exchange secondary ester functions for primary ester functions in aromatic esters, since treatment of *n*-butyl benzoates with tetra-(*sec*-butoxy)titanate permits[2087] exchange of the *sec*-butoxy group for the *n*-butoxy group in the ester (equation 1058). The authors claim[2087] that these transesterification reactions are less sensitive to inductive polar substituent effects than are their corresponding base-catalyzed counterparts and thus the transition state in the former reactions is less polar than in the latter reactions.

TABLE 97. Transesterification reactions catalyzed by phosphorus ylides[2083]

Esters	Alcohol	Catalyst	Time (h)	Temp. (°C)	Product	Yield (%)
MeCOOEt	MeOH	$Ph_3P{=}CHCH_2CN$	1	25	MeCOOMe	12
MeCOOEt	MeOH	$Ph_3P{=}CHCH_2CN$	0.5	30	MeCOOMe	34
MeCOOEt	MeOH	$Ph_3P{=}CHCH_2COOMe$	0.5	30	MeCOOMe	39
MeCOOEt	MeOH	$Ph_3P{=}CHCH_2COOEt$	0.5	30	MeCOOMe	44
MeCOOEt	MeOH	$(n\text{-}Bu)_3P{=}CHCH_2CN$	0.5	30	MeCOOMe	94
MeCOOEt	MeOH	$(n\text{-}Bu)_3P{=}CHCH_2COOMe$	0.5	30	MeCOOMe	93
MeCOOEt	MeOH	$(n\text{-}Bu)_3P{=}CHCH_2COOEt$	0.5	30	MeCOOMe	83
$ClCH_2COOEt$	MeOH	$Ph_3P{=}CHCH_2CN$	0.5	25	$ClCH_2COOMe$	100
$N{\equiv}CCH_2COOEt$	MeOH	$Ph_3P{=}CHCH_2CN$	1	25	$N{\equiv}CCH_2COOMe$	100
n-PrCOOEt	MeOH	$Ph_3P{=}CHCH_2CN$	1	25	—	0
PhCH=CHCOOEt (*trans*)	MeOH	$Ph_3P{=}CHCH_2CN$	24	25	PhCH=CHCOOMe (*trans*)	60
PhCOOEt	MeOH	$Ph_3P{=}CHCH_2CN$	24	25	PhCOOMe	15
p-AnCOOEt	MeOH	$Ph_3P{=}CHCH_2CN$	24	25	—	0
p-$O_2NC_6H_4COOEt$	MeOH	$Ph_3P{=}CHCH_2CN$	24	25	*p*-$O_2NC_6H_4COOMe$	71
EtOOC—COOEt	MeOH	$Ph_3P{=}CHCH_2CN$	0.25	25	EtOOC—COOMe	100
EtOOC—COOEt	MeOH	$Ph_3P{=}CHCH_2CN$	15	25	MeOOC—COOMe	100
n-PrOOC—COOPr-*n*	MeOH	$Ph_3P{=}CHCH_2CN$	15	25	MeOOC—COOMe	100
i-PrOOC—COOPr-*i*	MeOH	$Ph_3P{=}CHCH_2CN$	15	25	MeOOC—COOMe	100
$PhCH_2OOC—COOCH_2Ph$	MeOH	$Ph_3P{=}CHCH_2CN$	60	25	—	0

PhOOC—COOPh	MeOH	$Ph_3P{=}CHCH_2CN$	30	25	MeOOC—COOMe	100
t-BuOOC—COOBu-*t*	MeOH	$Ph_3P{=}CHCH_2CN$	60	25	—	0
MeOOC—COOMe	EtOH	$Ph_3P{=}CHCH_2CN$	60	25	EtOOC—COOEt	100
n-PrOOC—COOPr-*n*	EtOH	$Ph_3P{=}CHCH_2CN$	60	25	*n*-PrOOC—COOEt +	42
					EtOOC—COOEt	46
MeOOC—COOMe	*n*-PrOH	$Ph_3P{=}CHCH_2CN$	60	25	MeOOC—COOPr-*n* +	59
					n-PrOOC—COOPr-*n*	31
EtOOC—COOEt	*n*-PrOH	$Ph_3P{=}CHCH_2CN$	60	25	EtOOC—COOPr-*n* +	49
					n-PrOOC—COOPr-*n*	13
MeOOC—COOMe	*i*-PrOH	$Ph_3P{=}CHCH_2CN$	420	80	MeOOC—COOPr-*i* +	48
					i-PrOOC—COOPr-*i*	9
MeOOC—COOMe	*t*-BuOH	$Ph_3P{=}CHCH_2CN$	60	25	—	0
MeOOC—COOMe	PhOH	$Ph_3P{=}CHCH_2CN$	60	25	—	0
MeOOC—COOMe	$PhCH_2OH$	$Ph_3P{=}CHCH_2CN$	60	25	—	0
$CH_2(COOEt)_2$	MeOH	$Ph_3P{=}CHCH_2CN$	1	25	$EtOOCCH_2COOMe$ +	48
					$MeOOCCH_2COOMe$	29
$(CH_2)_2(COOEt)_2$	MeOH	$Ph_3P{=}CHCH_2CN$	1	25	$EtOOC(CH_2)_2COOMe$	18
EtOOCCH=CHCOOEt (*cis*)	MeOH	$Ph_3P{=}CHCH_2CN$	1	25	EtOOCCH=CHCOOMe (*cis*)	17
EtOOCCH=CHCOOEt (*trans*)	MeOH	$Ph_3P{=}CHCH_2CN$	1	25	EtOOCCH=CHCOOMe (*trans*)	100



(1057)

$$m\text{-}RC_6H_4COOBu\text{-}n + Ti(OBu\text{-}sec) \longrightarrow m\text{-}RC_6H_4COOBu\text{-}sec \qquad (1058)$$

$$R = H,\ Cl,\ NO_2$$

Thallium-containing compounds are another example of metal catalysts that may be used to effect transesterification reactions as illustrated by the reaction[2088] of various methyl esters with alcohols in the presence of thallium oxide (equation 1059). Other catalysts which have been used[2088] to effect this conversion include BaO, MoO_3 or a mixture of $BaO\text{–}Tl_2O_3\text{–}MoO_3$.

$$R^1COOMe + R^2OH \xrightarrow{Tl_2O_3} R^1COOR^2 \qquad (1059)$$

$R^1 = CH_2{=}CH,\ MeCH{=}CH,\ MeOOCCH{=}CH,\ H_2C{=}C(Me)$
$R^2 = \quad n\text{-Bu},\quad n\text{-Bu},\quad n\text{-Bu},\quad n\text{-Bu}$

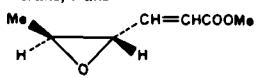
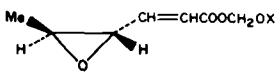
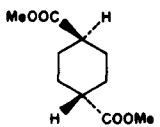
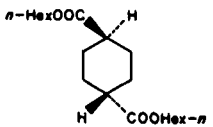
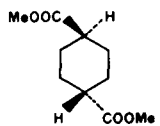
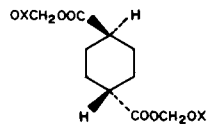
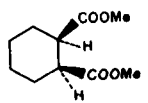
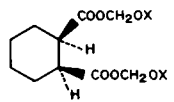
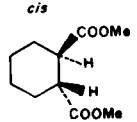
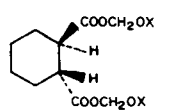
$R^1 = H_2C{=}C(Me),\ H_2C{=}C(Me)$
$R^2 = n\text{-}C_4H_9CH(Et)CH_2,\ Me_2NCH_2CH_2$

Thallium oxide, as well as a wide variety of other thallium compounds, has been reported[2089] to be very effective catalyst for the transesterification of alkyl esters of di-, tri- and tetracarboxylic acids with glycidol (2,3-epoxypropanol) and other alcohols as illustrated in equation 1060 and Table 98.

$$R^1COOH + R^2OH \xrightarrow[\text{conditions}]{\text{Tl catalyst}} R^1COOR^2 \qquad (1060)$$

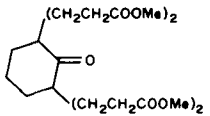
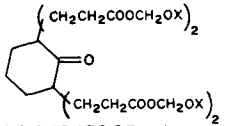
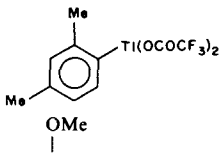
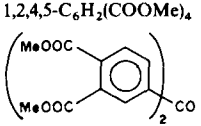
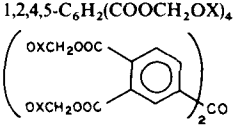
Trimethylsilyl esters of carboxylic acids have been reported[2090] to undergo transesterification by reaction with triphenylphosphine dibromide in dichloromethane. This initial reaction produces an intermediate acid bromide which is then treated with either an alcohol and 2-oxo-3-trimethylsilyltetrahydro-1,3-oxazole or a trimethylsilyl ether to produce the ester (equation 1061).

TABLE 98. Thallium-catalyzed transesterification reactions[2089]

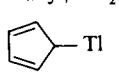
Esters[a]	Alcohols[a]	Catalyst[b]	Solvent	Temp. (°C)	Time (h)	Product[a]	Yield (%)
MeCOOEt	$OXCH_2OH$	$TlNO_3$	EtOH	73	6	$MeCOOCH_2OX$	48.2
n-PrCOOMe	$OXCH_2OH$	$Tl(OCOMe)_3$	Xylene	80	5	*n*-$PrCOOCH_2OX$	90.5
$OXCH_2OCH_2CH_2COOEt$	$OXCH_2OH$	Tl_2O_3	Xylene	80	12	$OXCH_2OCH_2CH_2COOCH_2OX$	53
MeCH=CHCH=CHCOOMe *trans, trans*	$OXCH_2OH$	Tl_2O_3	Xylene	80	38.5	$MeCH{=}CHCH{=}CHCOOCH_2OX$	62.5
 *trans,trans*	$OXCH_2OH$	Tl_2O_3	Xylene	80	36	 *trans,trans*	68.7
 *trans*	*n*-HexOH	TlOEt	Xylene	120	—	 *trans*	96
 *trans*	$OXCH_2OOCMe$	CpTl	Xylene	120	16	 *trans*	38
 *cis*	$OXCH_2OOCMe$	CpTl	Xylene	120	18	 *trans*	43.7
 *trans*	$OXCH_2OOCMe$	CpTl	Xylene	120	14	 *trans*	60

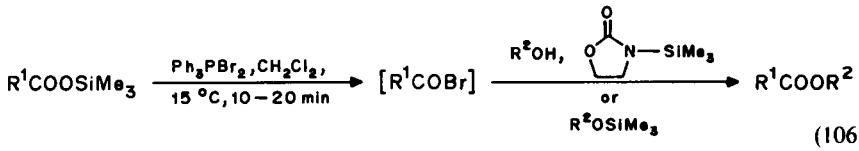
(continued)

TABLE 98. (*continued*)

Esters[a]	Alcohols[a]	Catalyst[b]	Solvent	Temp. (°C)	Time (h)	Product[a]	Yield (%)
	$OXCH_2OH$	$TlNO_3$	Xylene	80	14		99.7
$1,4\text{-}C_6H_4(COOMe)_2$	*n*-BuOH	Tl_2O_3	Xylene	80	—	$1,4\text{-}C_6H_4(COOBu\text{-}n)_2$	93
$1,4\text{-}C_6H_4(COOMe)_2$	*n*-BuOH	TlOEt	Xylene	80	—	$1,4\text{-}C_6H_4(COOBu\text{-}n)_2$	91
$1,4\text{-}C_6H_4(COOMe)_2$	*n*-BuOH		Xylene	80	—	$1,4\text{-}C_6H_4(COOBu\text{-}n)_2$	92
$1,4\text{-}C_6H_4(COOMe)_2$	*n*-BuOH	$PhCHCH_2Tl(OCOMe)_2$	Xylene	80	—	$1,4\text{-}C_6H_4(COOBu\text{-}n)_2$	93
$1,4\text{-}C_6H_4(COOMe)_2$	*n*-BuOH	CpTl	Xylene	80	—	$1,4\text{-}C_6H_4(COOBu\text{-}n)_2$	94
$1,4\text{-}C_6H_4(COOMe)_2$	MeCH(OH)Et	CpTl	Xylene	80	—	$1,4\text{-}C_6H_4(COOCHMeEt)_2$	93
$1,4\text{-}C_6H_4(COOMe)_2$	$OXCH_2OH$	Tl_2O_3	Xylene	80	14	$1,4\text{-}C_6H_4(COOCH_2OX)_2$	77.9
$1,4\text{-}C_6H_4(COOMe)_2$	$OXCH_2OH$	TlOCOMe	Xylene	110	—	$1,4\text{-}C_6H_4(COOCH_2OX)_2$	87
$1,4\text{-}C_6H_4(COOMe)_2$	$OXCH_2OH$	CpTl	Xylene	110	—	$1,4\text{-}C_6H_4(COOCH_2OX)_2$	86
$1,4\text{-}C_6H_4(COOMe)_2$	$OXCH_2OH$	$Tl(OCOCF_3)_3$	Xylene	110	—	$1,4\text{-}C_6H_4(COOCH_2OX)_2$	36
$1,2\text{-}C_6H_4(COOMe)_2$	$OXCH_2OH$	$Tl(OCOMe)_3$	Xylene	80	6.5	$1,2\text{-}C_6H_4(COOCH_2OX)_2$	98.6
$1,2\text{-}C_6H_4(COOMe)_2$	$OXCH_2OH$	CpTl	Xylene	110	—	$1,2\text{-}C_6H_4(COOCH_2OX)_2$	75
$1,3\text{-}C_6H_4(COOMe)_2$	$OXCH_2OH$	$TlNO_3$	Xylene	80	8	$1,3\text{-}C_6H_4(COOCH_2OX)_2$	90.6
$1,3,5\text{-}C_6H_3(COOMe)_3$	$OXCH_2OH$	Tl_2O_3	Xylene	80	9	$1,3,5\text{-}C_6H_3(COOCH_2OX)_3$	91.2
$1,2,4\text{-}C_6H_3(COOMe)_3$	$OXCH_2OH$	Tl_2O_3	Xylene	80	22	$1,2,4\text{-}C_6H_3(COOCH_2OX)_3$	86.1
$1,2,4,5\text{-}C_6H_2(COOMe)_4$	$OXCH_2OH$	Tl_2O_3	Xylene	80	12	$1,2,4,5\text{-}C_6H_2(COOCH_2OX)_4$	100
$1,2,4,5\text{-}C_6H_2(COOMe)_4$	$OXCH_2OH$	CpTl	Xylene	100	—	$1,2,4,5\text{-}C_6H_2(COOCH_2OX)_4$	75
	$OXCH_2OH$	Tl_2O_3	Xylene	80	14		84

[a] OX = oxiranyl,

[b] CpTl = 



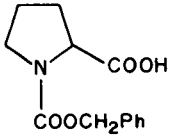
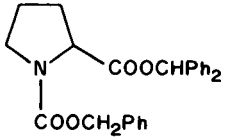
(1061)

R^1	R^2	Temp. (°C)	Time (h)	Yield (%)
Et	Ph	15	15	84
$PhCH_2CH_2$	$PhCH_2$	15	15	71
$H_2C{=}CMe$	*i*-Pr	15	15	75
$Me_2C{=}CH$	Et	15	15	70
$Me_2C{=}CH$	Et	15	15	90
$PhCH{=}CH$	Et	15	10	93
Ph	Me	15	15	85
$3,5\text{-}(O_2N)_2C_6H_3$	Me	10	10	98
PhCH[a]	Et	15	15	91[a]

[a]The diethyl ester, $PhCH(COOEt)_2$, is formed from the disilyl ether.

Another approach to transesterification is to react carboxylic acids and their salts with preformed inorganic esters. The products from these reactions are the organic esters and the inorganic acids. Several inorganic esters can be used to effect this type of ester exchange, but phosphate and sulfonate esters seem to be used most frequently. In the recent literature at least two reports of transesterification reactions using phosphate esters have appeared. These include the *O*-diphenylmethylation of carboxylic acids using diphenylmethyl diphenyl phosphate[2091] as the alkylating agent (equation 1062), and the use of diethyl trichloromethylphosphonate[2092] to produce ethyl esters of carboxylic acids (equation 1063).

(1062)

Acid	Time (min)	Product	Yield (%)
PhCOOH	40	$PhCOOCHPh_2$	86
CF_3COOH	1	$CF_3COOCHPh_2$	76
$PhCONHCH_2COOH$	180	$PhCONHCH_2COOCHPh_2$	92
	90		90

A report[2093] of sulfonate esters used in transesterification reactions describes the treatment of the ethyl di(isopropyl)ammonium salt of carboxylic acids with 4-bromo-2-

$$RCOOH + (EtO)_2P(O)CCl_3 \xrightarrow{CCl_4} RCOOEt \qquad (1063)$$

Acid	Temp. (°C)	Time (h)	Yield (%)
HCOOH	120	24	82
MeCOOH	120	8	77
MeCOOH	120	24	93
EtCOOH	120	24	98
i-BuCOOH	120	24	98
F_3CCOOH	90	24	52
Cl_3CCOOH	120	24	77
PhCOOH	120	24	96
o-TolCOOH	120	24	94
o-HOC_6H_4COOH	120	24	72
2,4,6-$Me_3C_6H_2COOH$	120	24	93

hydroxyacetophenone trifluoromethanesulfonate (4-bromophenacyl triflate) to produce the 4-bromophenacyl esters of the carboxylic acids (equation 1064).

$$RCO\overset{\ominus}{O}\ (i\text{-}Pr)_2\overset{\oplus}{N}HEt + p\text{-}BrC_6H_4COCH_2OSO_2CF_3 \xrightarrow[1\text{-}5\,min]{MeCN,\ 3^\circ\ amine} RCOOCH_2COC_6H_4Br\text{-}p \qquad (1064)$$

R = Me, Et, *n*-Pr, *n*-Bu, *n*-Pen, *n*-Hex, *n*-C_7H_{15}, *n*-C_8H_{17}, *n*-C_9H_{19}, *n*-$C_{10}H_{21}$, *n*-$C_{15}H_{31}$, *n*-$C_{17}H_{35}$, $BrCH_2$, Cl_3C, $HOOC(CH_2)_n$ ($n = 2$–10), *c*-C_3H_5, Me_3C, $HOOCCMe_2$, $HOOCCH_2CMe_2$, 2,4,6-$Me_3C_6H_2$, $HOCH_2$, $MeCHOHCH_2$

RCOOH = citric, aconitic, valproic, lactic, malic, salicylic and deoxycholic.

The reaction of preformed esters with acids to effect transesterification may also be applied to the treatment of carboxylic acid esters with carboxylic acids. Recently this approach has been applied to the methyl ester of trichloroacetic acid and the vinyl esters of acetic acid. With the former, the reaction was accomplished[2094,2095] with the use of an initiator in 18-crown-6 as solvent at 150 °C (equation 1065), while with the latter the reaction was accomplished using mercuric[2096] or palladium[2097–2099] acetate as catalysts (equation 1066).

$$PhCOOH + Cl_3CCOOMe \xrightarrow[\substack{18\text{-crown-6}\\150\,^\circ C,\ 3\,h}]{K_2CO_3,} PhCOOMe \qquad (1065)$$

$$R^1COOH + R^2COOCH{=}CH_2 \xrightarrow[Conditions]{Cat.} R^1COOCH{=}CH_2 \qquad (1066)$$

R^1	R^2	Cat.	Conditions	Reference
$CH_2{=}CH$, $CH_2{=}CMe$, $MeCH{=}CH$, *n*-Pr, $ClCH_2$, $PhCH{=}CH$	H, Me, *n*-Pr, cyclopropyl	$Pd(OAc)_2$	KOAc, 65 °C, 2 h	2097

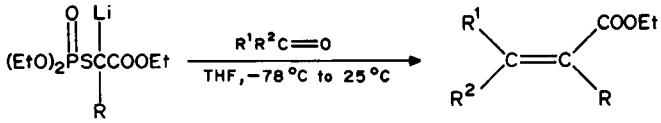
R^1	R^2	Cat.	Conditions	Reference
Et, CH_2=CH, CH_2=CMe, Ph	H, alkyl	$Pd(OAc)_2$	KOH, 50 °C, stir 7 h	2098
Et, Ph	Me	$Pd(OAc)_2$	KOAc, $Cu(OAc)_2$, KBr, 60 °C, 48 h	2099
$Ph(CH_2)_7$, $Ph(CH_2)_8$	Me	$Hg(OAc)_2$	48% HF, NaOAc, reflux 3 h	2096

*B. Esters by Condensation Reactions

*3. *Wittig-type reactions*

Among the recent applications of Wittig-type reactions to the preparation of α,β-unsaturated esters, the following examples represent either significant departures from traditional methods or synthetic transformations which are difficult with conventional Wittig chemistry.

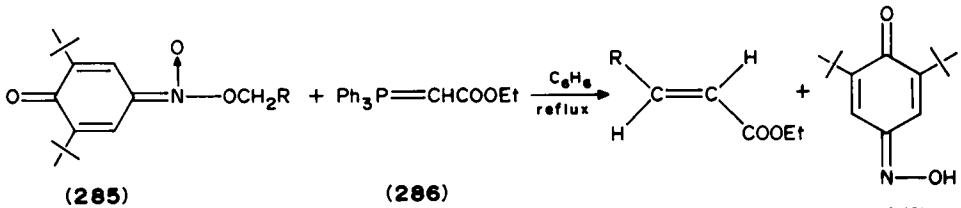
Lithium enolates of *S*-1-ethoxycarbonyl-2-alkyl diethyl phosphorothioates **284** have been found to be particularly useful for preparing trisubstituted α,β-unsaturated esters (equation 1067)[2100].



(1067)

(**284**) R=Me or n-C_3H_7

(*E*)-α,β-unsaturated esters can be synthesized by reaction of *aci*-nitroesters (**285**), prepared from 2,6-di-*tert*-butyl-4-nitrophenol and primary alcohols, with ethoxycarbonylmethylenetriphenylphosphorane (**286**) (equation 1068)[2101]. This procedure allows



(**285**) (**286**)

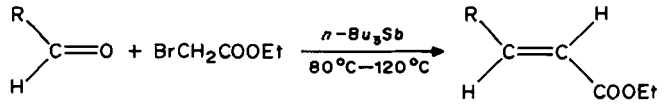
(1068)

alcohols rather than aldehydes to serve as the electrophilic component in olefination reactions, a decided advantage in terms of relative availability and stability.

Dialkyltelluronium carbethoxymethlides (**287**, R = Me or *n*-Bu) have been found to condense with a wide variety of aromatic aldehydes and ketones to give mainly (*E*)-α,β-unsaturated esters in good yields (equation 1069)[2102].

$$\underset{(\mathbf{287})}{R_2\overset{\oplus}{T}e\text{-}\overset{\ominus}{C}HCOOEt} + R^1R^2C{=}O \xrightarrow[-20\,^\circ C]{THF} R^1R^2C{=}CHCOOEt \qquad (1069)$$

Reaction of ethyl bromoacetate with aldehydes in the presence of an equimolar amount of tri-*n*-butylstibine results in olefination of the carbonyl compound to form (*E*)-α,β-unsaturated esters (equation 1070)[2103]. Ketones react also, but higher temperatures are required and yields are somewhat lower than with aldehydes. This one-pot reaction does not require base and can be carried out in a variety of solvents under neutral conditions.



(1070)

4. Reformatsky reaction

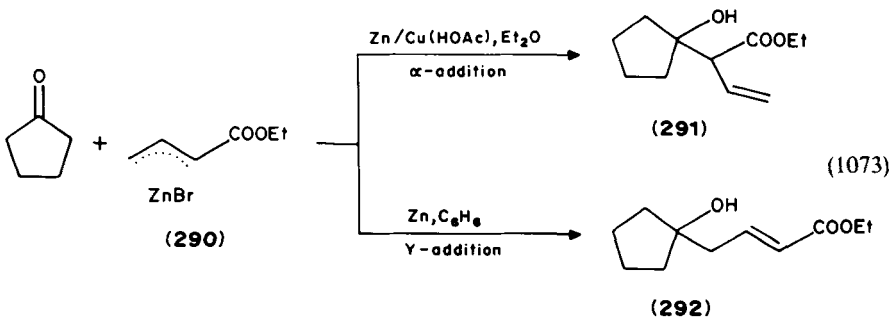
In a recent variation of the classical Reformatsky reaction, triethyl (carboethoxymethyl)tin (**288**) was found to add smoothly to aldehydes in the presence of tetramethylammonium fluoride (2 mole %) in dimethylsulfoxide to give good yields of β-hydroxy esters (equation 1071)[2104]. Reactions of the related tin reagent **289** with α,β-unsaturated aldehydes under similar conditions lead exclusively to 1,2-adducts with essentially no stereoselectivity (equation 1072). Reaction of **289** with benzaldehyde can be controlled by the choice of solvent and temperature to give either *erythro*-ethyl 2,3-diphenyl-3-hydroxypropionate. Also, tin reagents related to **288** or **289**, but derived from nitriles and/or *N*,*N*-dimethylcarboxamides, react with aldehydes to afford β-hydroxy nitriles and β-hydroxy amides, respectively[2104].

$$\underset{\textbf{(288)}}{Et_3SnCH_2COOEt} + RCHO \xrightarrow[DMSO,\ 20\,^{\circ}C]{Me_4\overset{\oplus}{N}F^{\ominus}} \xrightarrow[KF]{H_2O} RCH(OH)CH_2COOEt \qquad (1071)$$

$$\underset{\textbf{(289)}}{Me_3SnCHPhCOOEt} + RCH{=}CHCHO \longrightarrow RCH{=}CHCH(OH){-}CH(Ph)COOEt \qquad (1072)$$

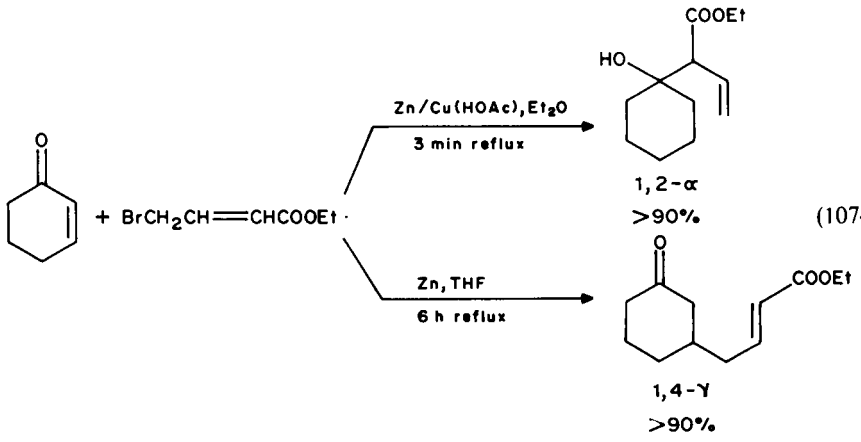
erythro:*threo* = 1:1

The ambident organozinc reagent **290** derived from ethyl 4-bromocrotonate reacts with simple ketones such as cyclopentanone to give hydroxy esters, **291** and **292** resulting from α- and γ-addition, respectively (equation 1073)[2105]. The regiochemistry of these reactions

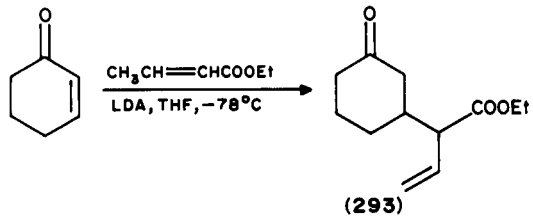


(1073)

was found to depend on the polarity of the solvent and the nature of zinc catalyst. In an extension of this study, reactions of **290** with a series α,β-unsaturated ketones and aldehydes were examined. The results obtained with 2-cyclohexenone are representative of the regiochemistry observed with enones, i.e. 1,2-α-addition of **290** prepared from zinc-copper couple containing traces of acetic acid, and 1,4-γ-addition of **290** prepared from acid-free zinc (equation 1074)[2106]. In contrast to these results, the lithium dienolate of ethyl crotonate reacts with 2-cyclohexenones to give mainly 1,4-α-product **293** (equation 1075)[2106].



(1074)



(1075)

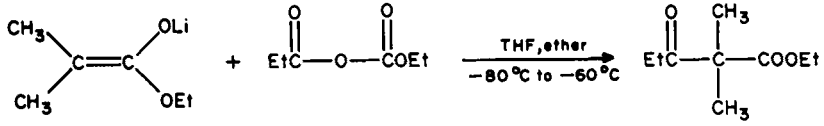
*7. *From α-anions of esters*

Ester enolates continue to find extensive use in the synthesis of elaborated esters and other carboxylic acid derivatives because of their versatility and ease of formation. The following examples represent some recent applications of these important synthetic intermediates.

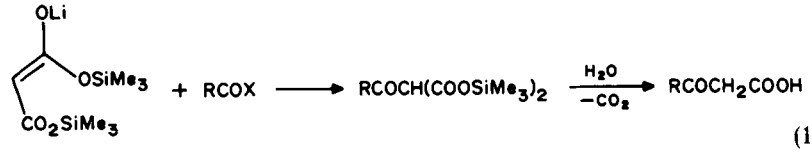
α-Alkylated esters can be prepared via copper enolates by allowing α-bromoesters to react with alkyllithium homocuprates followed by alkyl halides. The preparation of ethyl 2-ethylpentanoate (61%) from ethyl 2-bromopentanoate shown in equation 1076 is typical of this procedure, which also can be applied to α-bromoacids[2107].

$$CH_3CH_2CH_2CHBrCOOEt \xrightarrow[2.\ EtBr]{1.\ Et_2CuLi} CH_3CH_2CH_2CHEtCOOEt \quad (1076)$$

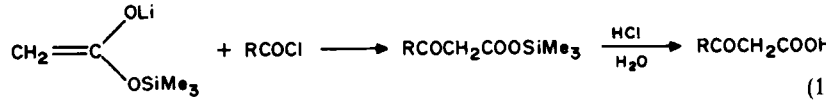
β-Keto esters are available by acylation of ester lithio enolates with mixed carboxylic and carbonic acid anhydrides (equation 1077)[2108]. β-Keto acids are conveniently synthesized employing either the lithium enolate of bis(trimethylsilyl) malonate (equation 1078)[2109] or the lithium enolate of trimethylsilyl acetate (equation 1079)[2110].



76% (1077)



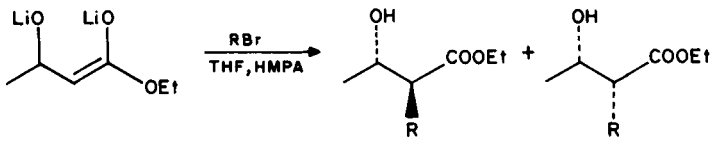
(1078)



(1079)

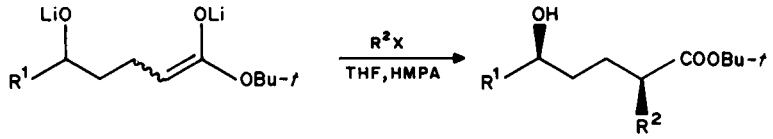
Dianions **294** derived from β-hydroxyesters by means of LDA undergo stereospecific alkylations to give mainly *threo*-α-alkyl-β-hydroxyesters **295** (equation 1080)[2111]. Alkylations of dianions **296**, generated from δ-hydroxy esters with lithium diethylamide, also proceed with a high degree of stereoselectivity to afford predominately *syn*-α-alkylated δ-hydroxy esters **297** (equation 1081)[2112].

Alkylations of lithio derivatives of chiral imidate esters proceed in good chemical yields and with high asymmetric induction to afford, on alcoholysis of the product imidate, chiral α,α-dialkylcarboxylic esters[2113]. The specific example shown in equation 1082 is representative of this procedure.

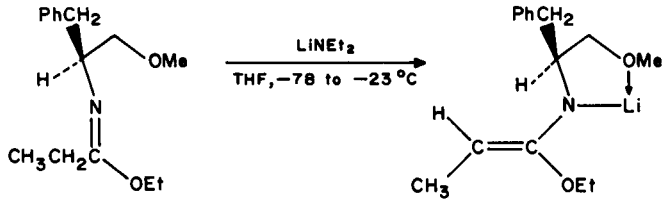


(1080)

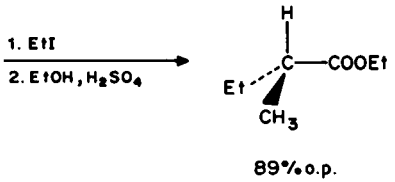
(294)	*threo*-(295)	*erythro*-(295)
R=CH_2=CH_2CH_2	96%	4%
R=$PhCH_2$	98%	2%
R=*n*-Bu	97%	3%



(296) (297) (1081)

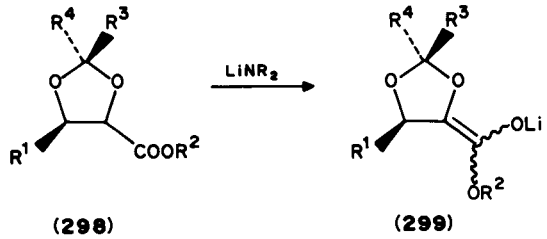


(1082)

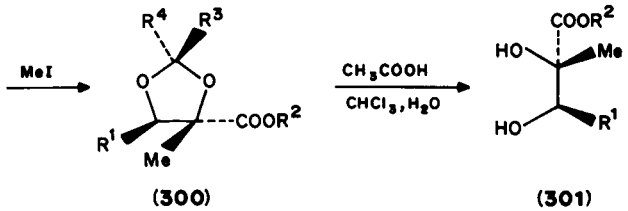


89% o.p.

Treatment of alkyl 1,3-dioxolane-4-carboxylates (**298**) with lithium dialkylamides gives enolates **299**, which undergo stereoselective alkylation with methyl iodide to give mainly *syn* products **300**. Deketalization of **300** then affords *erythro*-α,β-dihydroxy esters **301** (equation 1083)[2114].

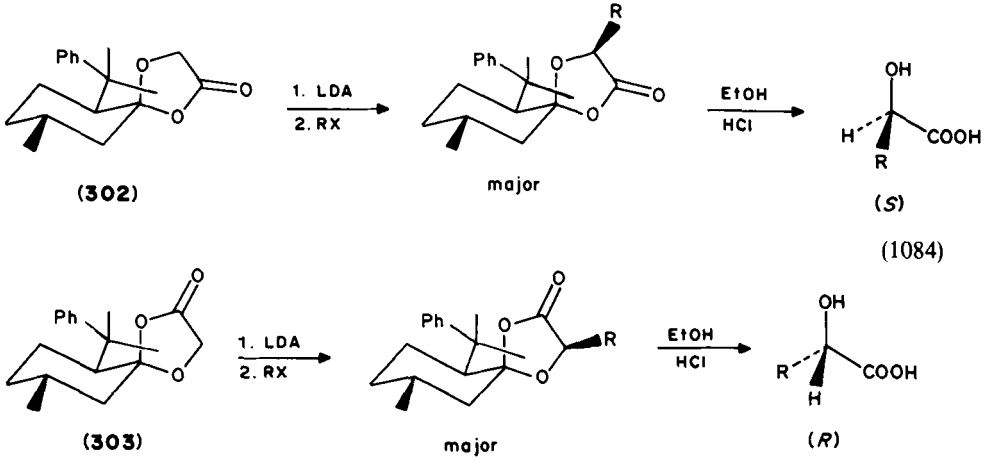


(298) (299) (1083)



(300) (301)

Spiro-fused 1,3-dioxolan-4-ones **302** and **303**, prepared by ketalization of optically active 8-phenylmenthone with trimethylsilyl trimethylsilyloxyacetate, serve as sources of chiral glycolate enolate equivalents upon deprotonation with LDA. Alkylation of the respective enolates proceeds with high diastereoselectivity to provide either enantiomer of the corresponding α-alkyl α-hydroxy esters (equation 1084)[2115].



(1084)

Reaction of the magnesium enolate of *tert*-butyl acetate with various nitriles provides a convenient route to β-aminoacrylate esters (equation 1085)[2116].

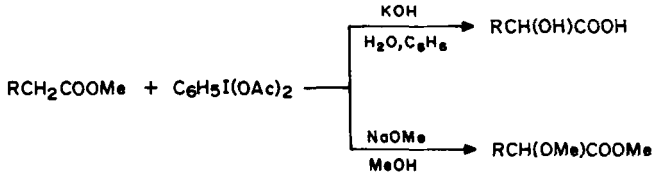
$$CH_3COOBu\text{-}t \xrightarrow[2.\ RCN]{1.\ Mg[NCH(CH_3)_2]_2,\ Et_2O} H_2NCR{=}CHCOOBu\text{-}t \qquad (1085)$$

3-Alkoxycrotonates yield delocalized enolates on treatment with sodium amide in DMF or HMPA. These anions react regiospecifically at the γ-position with aldehydes and ketones to form dienoic acids via a lactone intermediate (equation 1086)[2117].

$$CH_3C(OR){=}CHCOOEt + R^1R^2C{=}O \xrightarrow[DMF\ or\ HMPA]{NaNH_2}$$

$$R^1R^2C{=}CH{-}C(OR){=}CHCOOH \qquad (1086)$$

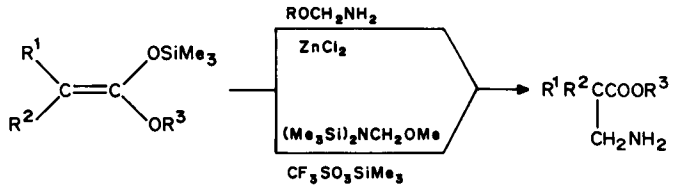
Treatment of aryl and alkyl carboxylate esters with phenyliodosodiacetate in the presence of potassium hydroxide or sodium methoxide affords α-hydroxy acids and α-methoxy esters, respectively, in a process which is assumed to involve initial reaction of the ester enolate with the hypervalent iodine reagent (equation 1087)[2118].



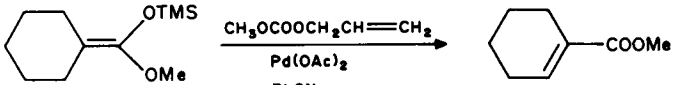
(1087)

O-Silyl ketone acetals can act as ester enolate equivalents through reactions with electrophilic reagents, usually in the presence of a Lewis acid catalyst. For example, ketene trimethylsilyl acetals react with *tert*-butyl chloride using zinc chloride as catalyst to afford α-*tert*-butylated esters (equation 1088)[2119]. Reactions of *O*-silyl ketene acetals with aminomethyl ethers in the presence of zinc chloride[2120] or with *N*,*N*-bis(trimethylsilyl)methoxymethylamine in the presence of trimethylsilyl triflate[2121] afford α-aminomethyl esters[2120,2121] and lactones (equation 1089)[2120]. A convenient method for synthesizing α,β-unsaturated esters involves conversion of the ester to the corresponding ketene trimethylsilyl acetal followed by treatment with an allyl carbonate in the presence of palladium acetate (equation 1090)[2122]. Conversions of ketones to α,β-unsaturated ketones and lactones to α,β-unsaturated lactones can be effected similarly[2122]. Reaction of tris(trimethylsilyloxy)ethene (**304**) with aldehydes in the presence of tin(IV) chloride followed by acidic hydrolysis of the reaction mixture affords 2,3-dihydroxy acids (equation 1091)[2123].

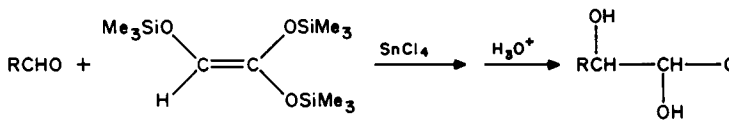
$$R^1R^2C{=}C(OEt)OSiMe_3 + t\text{-BuCl} \xrightarrow[25\ ^\circ C]{ZnCl_2,\ CH_2Cl_2} \xrightarrow{H_3O^+} R^1R^2C(t\text{-Bu})COOEt \qquad (1088)$$



(1089)



(1090)

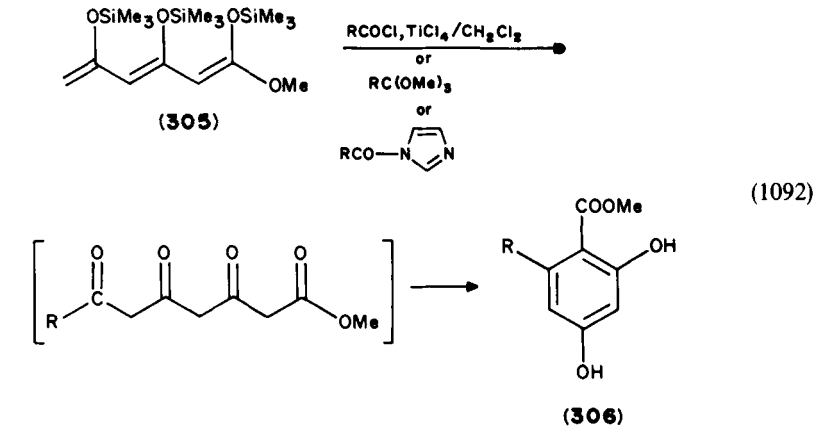


(1091)

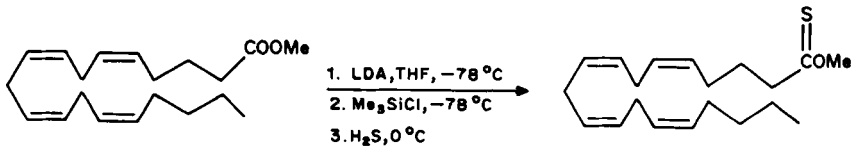
(304)

Reactions of tris(trimethylsilyloxyl)-1-methoxy-1,3,5-hexatriene (**305**) with electrophiles such as *ortho* esters, acid chlorides and imidazolides in the presence of titanium tetrachloride occur at the ε-position of **305** to give resorcinols **306** as a result of intramolecular aldol condensation (equation 1092)[2124].

O-Alkylthioesters can be synthesized conveniently from carboxylic esters by *in situ* preparation of the respective *O*-silyl ketene acetals followed by saturation of the reaction mixture with hydrogen sulfide (equation 1093)[2125]. This procedure can also be applied to γ-butyrolactone.



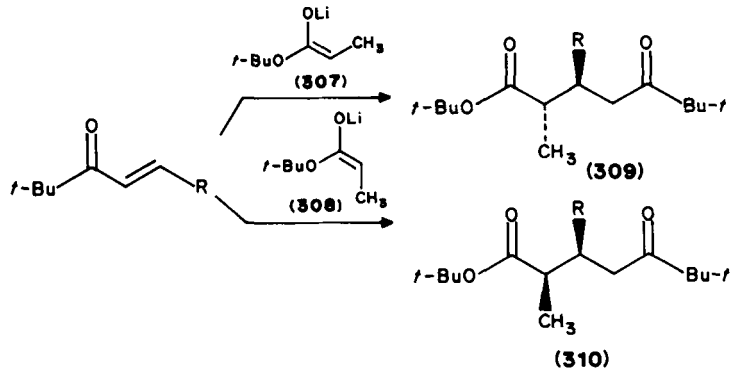
(1092)



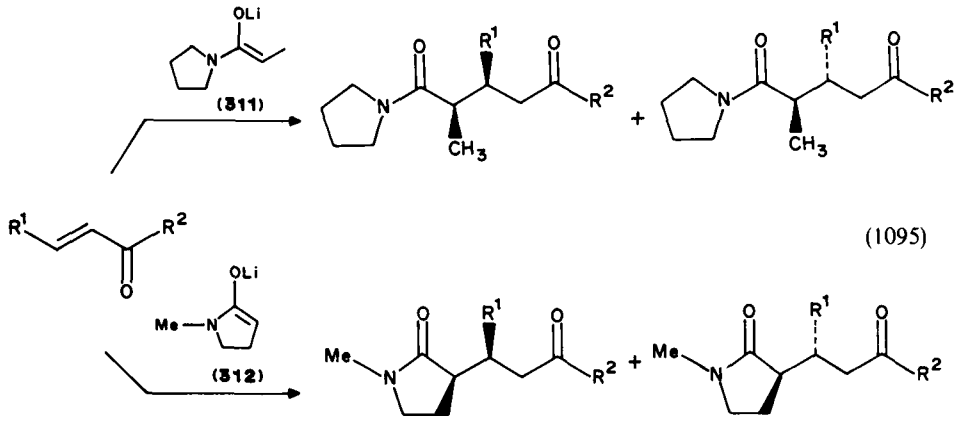
(1093)

*8. *Michael reactions and related conjugate additions*

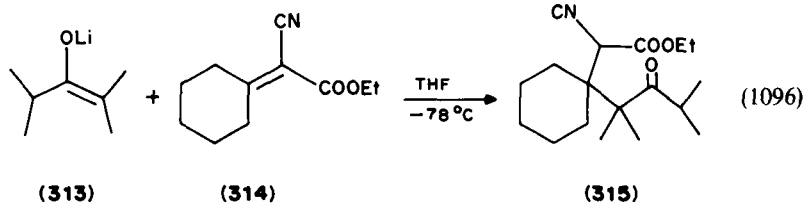
A recent study of the stereochemistry of the kinetically controlled Michael addition of *Z* (**307**) and *E* (**308**) enolates of *tert*-butyl propionate to a series of β-substituted enones has established that these reactions constitute a convenient, stereoselective synthesis of δ-keto esters possessing two stereocenters[2126]. Thus, reactions of enones with *Z* enolates **307** gives predominately the anti-δ-keto esters **309**, whereas conjugate of the *E* enolate **308** gives the *syn* isomers **310** (equation 1094). The *Z* (**311**) and *E* (**312**) enolates derived from *N*-propionylpyrrolidine and *N*-methylpyrrolidone, respectively, react similarly with enones, but the degree of stereoselectivity leading to the product δ-ketoamides is lower than that observed with ester enolates (equation 1095)[2127].



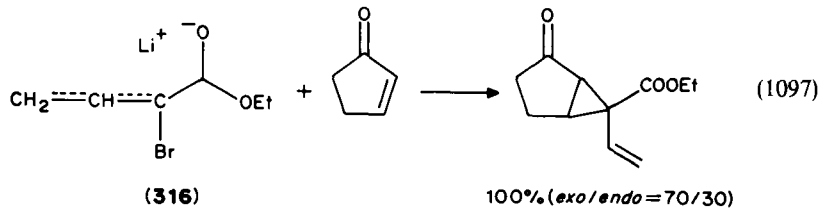
(1094)



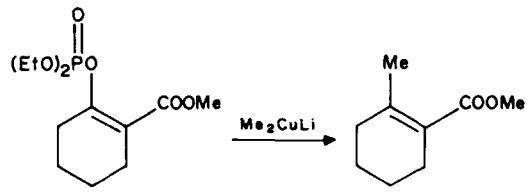
Until recently it has been observed that Michael additions carried out under aprotic conditions tended to proceed poorly with α,β-unsaturated acceptor molecules possessing two β-substituents. It has now been discovered that the steric hindrance at the β-position of Michael acceptors can be overcome by having *two* electron-withdrawing substituents present at the α-position. For example, the lithium enolate (**313**) of diisopropyl ketone reacts smoothly with α,β-unsaturated cyano ester **314** to form cyano ester **315** in 95% yield (equation 1096)[2128].



1,4-Addition of the lithium dienolate anion (**316**) of ethyl 2-bromocrotonate to α,β-enones provides a facile route to 1-vinylcyclopropane carboxylic esters as shown in equation 1097[2129].

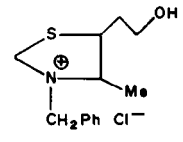


β-Alkyl-α,β-unsaturated esters can be prepared by reaction of lithium dialkylcuprates with α,β-unsaturated esters containing an appropriate leaving group at the β-position as illustrated by the synthesis of methyl 2-methyl-1-cyclohexene-1-carboxylate **318** from enolate phosphate **317** (equation 1098)[2130].



(317) (318) (1098)

In a process which may be viewed as 1,4-addition of aldehyde acyl anions to α,β-unsaturated esters, 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (**319**) catalyzes addition of aliphatic aldehydes to α,β-unsaturated esters to produce γ-ketocarboxylic esters (equation 1099)[2131].



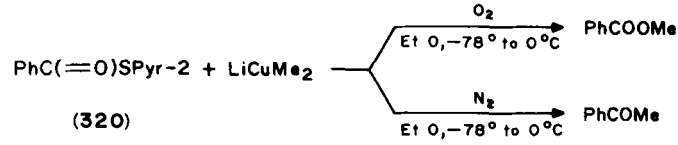
(319)

$$RCHO + CH_2{=}CHCOOEt \longrightarrow RCOCH_2CH_2COOEt \qquad (1099)$$

*D. Miscellaneous Ester Syntheses

4. From thioesters

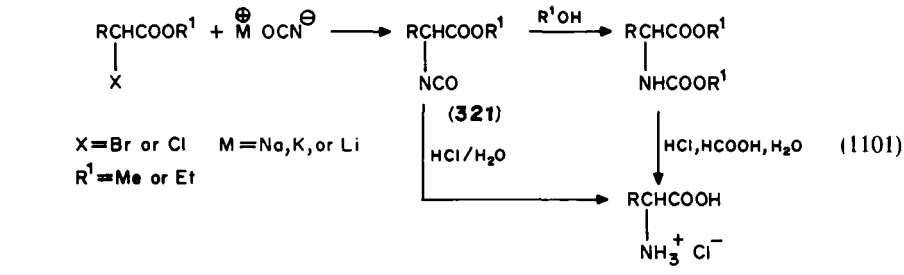
S-2-Pyridyl thioates (**320**) react with lithium dialkylcuprates under an oxygen atmosphere to form carboxylic esters (equation 1100)[2132]. However, when the reactions were conducted under nitrogen, ketones were produced.



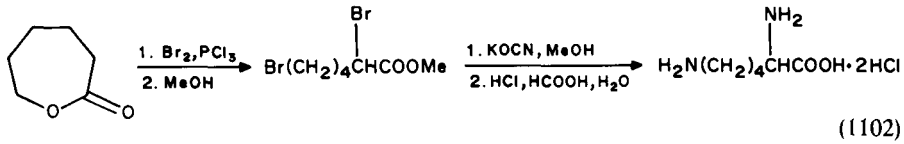
(1100)

5. From mono- and dihaloesters

Reactions of *tert*-butyl esters of α-halocarboxylic acids with liquid ammonia, methylamine, diethylamine, sodium methoxide, sodium phenoxide and (−)-menthol produce the corresponding α-substituted *tert*-butyl esters[2133]. α-Halogenated methyl and ethyl carboxylic esters react with alkali cyanates to yield α-isocyanato esters **321**, which can be converted to α-amino- or α-alkoxycarbonylamino acids by acid hydrolysis or alcoholysis, respectively (equation 1101)[2134]. The synthesis of DL-lysine[2134] from γ-caprolactone shown in equation 1102 represents a specific application of this procedure. Several patent disclosures describe the conversion of 3,4-dibromo esters into 4-bromo-2-



(1101)



(1102)

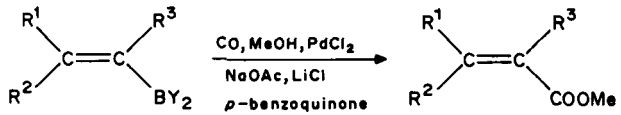
alkenoates by aqueous sodium hydroxide in the presence of quaternary ammonium salts[2135], crown ethers[2136] or polyethylene glycol (equation 1103)[2137].

$$CH_3CHBrCHBrCH_2COOEt + NaOH_{(aq)} \xrightarrow[\text{18-crown-6 or PEG}]{R_4N^+Cl^-} CH_3CHBrCH{=}CHCOOEt \quad (1103)$$

6. *Alkoxycarbonylation*

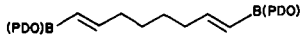
a. Of double and triple bonds. Reactions in which substrates of various compositions are treated with carbon monoxide and an alcohol to produce esters are referred to as alkoxycarbonylations. When the substrate so treated contains a double or triple bond, one class of reactions consists of substrates which, after the procedure, maintain their double or triple bonds in the product, while the second class of reactions consists of substrates which lose the multiple bond upon alkoxycarbonylation.

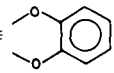
Reactions of substrates which maintain the double bond in the product will be discussed first, beginning with the palladium-catalyzed methoxycarbonylation of 1-alkenylboranes to produce[2138], the corresponding α,β-unsaturated methyl esters (equation 1104).



(1104)

Alkenylborane				Temp.	Time	Yield
R^1	R^2	R^3	Y_2[a]	(°C)	(h)	(%)
n-Bu	H	H	PDO	r.t.	2	92
H	*n*-Bu	H	$(Me_2CHCHMe)_2$	0	2	42
n-Bu	H	Me_3Si	PDO	50	2	87
Et	H	Et	PDO	50	2	95

Alkenylborane				Temp.	Time	Yield
R^1	R^2	R^3	Y_2[a]	(°C)	(h)	(%)
n-Hex	H	H	PDO	50	2	93
n-Hex	H	H	$(Me_2CHCHMe)_2$	r.t.	2	73
$HC{\equiv}C(CH_2)_4$	H	H	PDO	r.t.	2	66
Ph	H	H	PDO	50	2	70
Also:						
		$PhB(OH)_2$		r.t.	2	41
				r.t.	4	84

[a]PDO ≡ *o*-Phenylenedioxy ≡ 

The same palladium chloride–lithium chloride catalyst can also be used to effect[2139] alkoxycarbonylation of substituted vinyl mercuric chlorides (equation 1105).

$$R^1CH{=}CHHgCl + CO + R^2OH \xrightarrow[LiCl]{PdCl_2} \underset{(E)}{R^1CH{=}CHCOOR^2} \qquad (1105)$$

R^1 = *n*-Bu, Ph, *t*-Bu, *n*-C_8H_{17}, *c*-Hex, $(CH_2)_3CN$, $(CH_2)_8COOMe$, $CH_2{=}CMe$
R^2 = Me, Et

Treatment of allyl carbonates with carbon monoxide in the presence of palladium acetate and triphenylphosphine is also reported[2140] to produce an ester which retains the double bond (equation 1106).

$$H_2C{=}CMeCH_2OCOOEt + CO(10\ atm) \xrightarrow[Ph_3P,\ 50\,°C]{Pd(OAc)_2} H_2C{=}CMeCH_2COOEt \qquad (1106)$$

Alkoxycarbonylation of olefins which results in the loss of the double bond during the reaction to produce the ester product are catalyzed by a wide variety of reagents. Thus, treatment of propylene with carbon monoxide and methanol can be catalyzed by a mixture of boron trifluoride–desired ester complex, boron trifluoride–methanol reactant complex and copper tetracarbonyl[2141] (equation 1107).

$$MeCH{=}CH_2 + CO + MeOH \xrightarrow[BF_3{\cdot}Me_2CHCOOMe,\ Cu(CO)_4]{BF_3{\cdot}MeOH,} Me_2CHCOOMe \qquad (1107)$$

By using cobalt acetate in a pyridine–toluene solvent mixture, 3-pentenenitrile can be methoxycarbonylated to produce[2142] δ-cyanovalerate in 98% yield (equation 1108).

$$H_2C{=}CHCH_2CH_2CN + MeOH + CO(200\ bar) \xrightarrow[C_5H_5N,\ C_6H_5Me,\ 106\,°C,\ 4\,h]{Co(OAc)_2,} \underset{98\%}{MeOOCCH_2CH_2CH_2CH_2CN} \qquad (1108)$$

Another cobalt catalyst reported[2143] to effect alkoxycarbonylation is dicobalt octacarbonyl (equation 1109) in pyridine.

$$n\text{-}C_8H_{17}CH{=}CH_2 + MeOH + CO(20\,atm) \xrightarrow[\substack{C_5H_5N,\ MeCOCH-CH_2,\\ autoclave,\ 110\,^\circ C,\ 6\,h}]{CO_2(CO)_8,}$$

$$n\text{-}C_{10}H_{21}COOMe + n\text{-}C_8H_{17}CHMeCOOMe + \text{other products} \quad (1109)$$
$$81.4\% \qquad 14.6\% \qquad \text{in much smaller yields}$$

Numerous ligand-stabilized platinum(II)–Group 4B metal halide complexes have been reported[2144] to be effective as alkoxycarbonylation catalysts for α-olefins to produce their corresponding linear carboxylic acid esters (equation 1110).

$$R^1CH{=}CH_2 + R^2OH \xrightarrow[\substack{240\,atm.,\ CO,\\ 80\,^\circ C,\ 6\,h}]{\text{Pt-complex,}} R^1CH_2CH_2COOR^2 \quad (1110)$$

R^1 = Me, *n*-Pen, *n*-$C_{12}H_{25}$, *n*-$C_{18}H_{37}$, EtCHMe, Me_2CHCH_2
R^2 = Me, $ClCH_2CH_2$, Me_2CH, *n*-C_8H_{17}, Ph, EtSH[a]
Pt complex = $(Ph_3As)_2PtCl_2$-$SnCl_2$, $(Ph_3As)_2PtCl_2$-$SnCl_4$, $(Ph_2ClAs)_2PtCl_2$-$SnCl_2$, $(Ph_3As)_2PtCl_2$-$SbCl_3$, $(Ph_3As)_2PtCl_2$-$GeCl_2$, $(Ph_3As)_2PtCl_2$-$PbCl_2$, $(Ph_3As)_2PtI_2$-SnI_2, $(Ph_3As)_2PtCl_2$, $(Ph_3As)_2Pt(CN)_2$, $(Ph_3As)_2PtCl_2$-$SnCl_2$-$AsPh_3$, $[(PhO)_3P]_2PtCl_2$-$SnCl_2$, $[(p\text{-}ClC_6H_4)_3P]_2PtCl_2$-$SnCl_2$, $(Ph_3P)_2PtCl_2$-$SnCl_2$, $[p\text{-}MeOC_6H_4)_3P]_2PtCl_2$-$SnCl_2$, $(PhMe_2P)_2PtCl_2$-$SnCl_2$, $(Ph_3Sb)_2PtCl_2$-$SnCl_2$, $(Ph_2S)_2PtCl_2$-$SnCl_2$, $(Ph_3P)_4Pt$-$SnCl_2$, $(Ph_2As(CH_2)_2AsPh_2)PtCl$-$SnCl_2$, (1,10-phenanthroline)PtCl-$SnCl_2$

[a]The product using this substrate is ethyl thioloctanoate.

Palladium-containing compounds are the most widely used catalysts for the alkoxycarbonylation of olefins reported in the recent literature. They include the simple palladium chloride–copper chloride mixture in hydrochloric acid which was used[2145] to esterify 1-decene (equation 1111), and the palladium chloride–tetra-*n*-butyl ammonium chloride mixture in hydrochloric acid to esterify butadiene[2146] (equation 1112).

$$n\text{-}C_8H_{12}CH{=}CH_2 + MeOH + CO \xrightarrow[HCl]{PdCl_2,\ CuCl_2,} Me(CH_2)_7CHMeCOOMe \quad (1111)$$

$$CH_2{=}CH{-}CH{=}CH_2 + EtOH + CO \xrightarrow[(n\text{-}Bu)_4NCl]{PdCl_2,\ HCl} MeCH{=}CHCH_2COOEt$$
$$+ CH_2{=}CHCHMeCOOEt + CH_2{=}CH(CH_2)_3CH{=}CHCH_2COOEt \quad (1112)$$
$$+ EtOOCCH_2CH_2CHMeCOOEt + \text{other products in low yields}$$

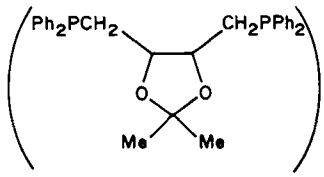
Two additional reports of the use of palladium-containing catalysts for alkoxycarbonylation reactions address the regioselectivity and regiospecificity concerns associated with these reactions. In 1976, Consiglio and Marchetti reported[2147] that the regiospecificity of the alkoxycarbonylation reactions which are catalyzed by palladium-containing catalysts is strongly ligand-dependent, and that for aromatic olefins the regiospecificity of 2,2-dimethyl-4,5-bis(diphenylphosphinomethyl)-1,3-dioxolane palladium dichloride (**322**) and bis(triphenylphosphine) palladium dichloride (**323**) are opposite.

TABLE 99. Palladium-catalyzed alkoxycarbonylation of olefins[2147]

Olefin	Catalyst[a]	Alcohol	Solvent	Press CO (atm)	Product	Isomer ratio straight/ branched chain
$MeCH{=}CH_2$	$(Ph_3P)_2PdCl_2$	EtOH	C_6H_6	700[b]	$MeCH_2CH_2COOEt$ + $Me_2CHCOOEt$	30/60
$MeCH{=}CH_2$	2(DIOP) + 1 $PdCl_2$	MeOH	—	720	$MeCH_2CH_2COOMe$ + $Me_2CHCOOMe$	64/36
$EtCH{=}CH_2$	$(Ph_3P)_2PdCl_2$	EtOH	—	460	$EtCH_2CH_2COOEt$ + $EtCHMeCOOEt$	44/56
$EtCH{=}CH_2$	2(DIOP) + 1 $PdCl_2$	EtOH	—	450	$EtCH_2CH_2COOEt$ + $EtCHMeCOOEt$	25/75
$n\text{-}C_{10}H_{21}CH{=}CH_2$	$(Ph_3P)_2PdCl_2$	EtOH	—	410	$n\text{-}C_{10}H_{21}CH_2CH_2COOEt$ + $n\text{-}C_{10}H_{21}CHMeCOOEt$	49/51
$n\text{-}C_{10}H_{21}CH{=}CH_2$	2(DIOP) + 1 $PdCl_2$	EtOH	—	380	$n\text{-}C_{10}H_{21}CH_2CH_2COOEt$ + $n\text{-}C_{10}H_{21}CHMeCOOEt$	67/33
$n\text{-}C_{10}H_{21}CH{=}CH_2$	$Ph_2P(CH_2)_4PPH_2PdCl_2$	EtOH	—	390	$n\text{-}C_{10}H_{21}CH_2CH_2COOEt$ + $n\text{-}C_{10}H_{21}CHMeCOOEt$	67/33
$PhCH{=}CH_2$	$(Ph_3P)_2PdCl_2$	EtOH	C_6H_6	390	$PhCHMeCOOEt$	0/100
$PhCH{=}CH_2$	$[Ph_2PCH_2CHMeEt]_2PdCl_2$	EtOH	C_6H_6	390	$PhCHMeCOOEt$	0/100
$PhCH{=}CH_2$	$(DIOP)PdCl_2$	EtOH	C_6H_6	390	$PhCH_2CH_2COOEt$ + $PhCHMeCOOEt$	40/60
$PhCH{=}CH_2$	2(DIOP) + 1 $PdCl_2$	EtOH	C_6H_6	390	$PhCH_2CH_2COOEt$ + $PhCHMeCOOEt$	54/46

$PhCH{=}CH_2$	2(DIOP) + 1 $PdCl_2$	MeOH	—	460	$PhCH_2CH_2COOMe$ + $PhCHMeCOOMe$	80/20
$PhCMe{=}CH_2$	$(Ph_3P)_2PdCl_2$	EtOH	C_6H_6	390	$PhCHMeCH_2COOEt$ + $PhCMe_2COOEt$	2/98
$PhCMe{=}CH_2$	$[Ph_2PCH_2CHMeEt]_2PdCl_2$	EtOH	C_6H_6	380	$PhCHMeCH_2COOEt$ + $PhCMe_2COOEt$	3/97
$PhCMe{=}CH_2$	$PdCl_2 + 2\,PPh_2$ (neomethyl)	EtOH	C_6H_6	400	$PhCHMeCH_2COOEt$ + $PhCMe_2COOEt$	1/99
$PhCMe{=}CH_2$	(DIOP)$PdCl_2$	EtOH	C_6H_6	390	$PhCHMeCH_2COOEt$ + $PhCMe_2COOEt$	96/4
$PhCMe{=}CH_2$	2(DIOP) + 1 $PdCl_2$	EtOH	C_6H_6	390	$PhCHMeCH_2COOEt$ + $PhCMe_2COOEt$	99/1

[a]DIOP = **322.**
[b]Temperature used, 90 °C.



(DIOP)$PdCl_2$

(322)

$PdCl_2$ $(Ph_3P)_2PdCl_2$

(323)

This means that when **322** was used as the catalyst a higher proportion of straight-chain to branched-chain ester was obtained, while when **323** was used a higher ratio of branched-chain to straight-chain ester isomers was obtained (Table 99). With styrene and α-methylstyrene and **323**, formation of the branched-chain isomers takes place almost exclusively, while with **322** and α-methylstyrene only the straight-chain isomer is formed but, with styrene, a great prevalence of ethyl 3-phenylpropionate is formed (Table 99). Finally, when aliphatic olefins are alkoxycarbonylated using **322** and **323**, the regiospecificity trends associated with each catalyst system are the same as that observed with aromatic olefins but are less pronounced (Table 99). Equation 1113 presents the general reaction to which the information in Table 99 applies.

$$R^1R^2C{=}CH_2 + R^3OH + CO \xrightarrow[100\ ^\circ C]{\text{Pd Cat.}} R^1R^2CHCH_2COOR^3 + R^1R^2CMeCOOR^3 \quad (1113)$$

The second report[2148] describes the regioselectivity involved in the alkoxycarbonylation of 1-alkenes when the reaction is catalyzed by dispersions of ligand-stabilized palladium(II) chlorides in quaternary Group VB salts of trichlorostannate(II) (equation 1114). The results of these reactions, reported in Table 100, indicate the sensitivity of these syntheses to the composition of the catalyst and the structure of the alkene.

$$R^1CH{=}CH_2 + R^2OH + CO \xrightarrow[\substack{\text{salt,}\\ \text{autoclave}}]{\text{Pd cat.,}} R^1CH_2CH_2COOR^2 + R^1CHMeCOOR^2 \quad (1114)$$

Alkoxycarbonylation of olefins has also been reported[2149] to occur in the presence of a nickel iodide–molybdenum hexacarbonyl-ethyl iodide catalyst, using triphenylphosphine as a promoter and ethyl propionate as solvent (equation 1115).

$$CH_2{=}CH_2 + CO + MeOH \xrightarrow[Ph_3P,\ MeCH_2COOEt]{NiI/Mo(CO)_6,\ EtI} MeCH_2COOMe \quad (1115)$$

At least one report of the alkoxycarbonylation of a terminal acetylene which retains its triple bond in the ester product produced appears in the recent literature[2150]. The reaction conditions used to effect this transformation are very mild and involve[2150] treatment of the acetylene with alcohol and carbon monoxide at 1 atmosphere in the presence of a catalytic amount of palladium chloride and a stoichiometric amount of copper chloride in the presence of sodium acetate at room temperature (equation 1116). The mechanism proposed[2150] for this conversion involves the oxidative carbonylation of the acetylene with Pd^{2+}, which is reduced to Pd^0 and which is subsequently reoxidized by the copper chloride, while the base present serves as an acid trap for the hydrogen chloride formed.

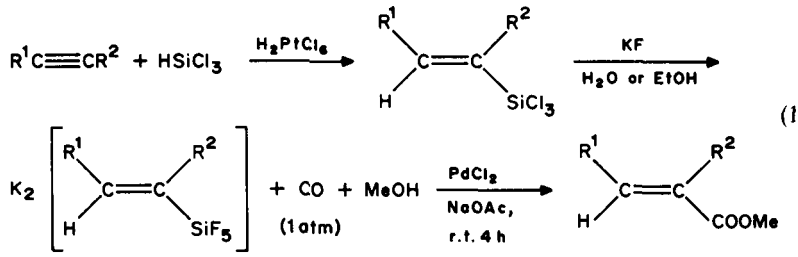
$$R^1C{\equiv}CH + CO\ (1\ atm) + R^2OH \xrightarrow[\substack{CuCl_2,\\ NaOAc\\ r.t.}]{PdCl_2,} R^1C{\equiv}CCOOR^2 \quad (1116)$$

Acetylene	Alcohol	Catalyst	Base	Time (h)	Product	Yield (%)
PhC≡CH	MeOH	A	NaOAc	2	PhC≡CCOOMe	74
PhC≡CH	MeOH	B	None	10	PhC≡CCOOMe	70
PhC≡CH	MeOH	C	NaOAc	5	PhC≡CCOOMe	70
PhC≡CH	MeOH	A	KOAc	2	PhC≡CCOOMe	58
PhC≡CH	*i*-PrOH	A	NaOAc	2	PhC≡CCOOPr-*i*	67
n-PenC≡CH	MeOH	A	NaOAc	2	*n*-PenC≡CCOOMe	74
n-PenC≡CH	*i*-PrOH	A	NaOAc	2	*n*-PenC≡CCOOPr-*i*	59
$PhOCH_2C{\equiv}CH$	MeOH	A	NaOAc	2	$PhOCH_2C{\equiv}CCOOMe$	60

A: 1 mmole acetylene, 0.056 mmole $PdCl_2$, 2 mmole $CuCl_2$, 2 mmole base.
B: 1 mmole acetylene, 0.056 mmole $Pd(OAc)_2$, 1 mmole *p*-benzophenone.
C: 1 mmole acetylene, 0.011 mmole $PdCl_2$, 2 mole $CuCl_2$, 2 mmole base.

In some alkoxycarbonylations of molecules containing terminal acetylene bonds the latter are reduced to double bonds in the ester product formed. In one report[2151] the regioselectivity involved in the alkoxycarbonylation of 1-alkynes in the presence of ligand stabilized palladium(II)–tin(II) chloride complexes to produce α,β-unsaturated acid esters is discussed (equation 1117 and Table 101).

$$R^1C{\equiv}CR^2 + CO + R^3OH \xrightarrow[\text{temp}\\ \text{autoclave}]{\text{cat., time}} R^1C{=}CR^2COOR^3 \qquad (1117)$$



(1118)

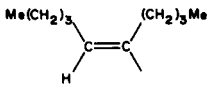
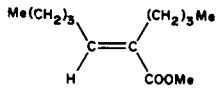
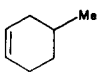
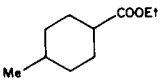
R in $K_2[RSiF_5]$	Product	Yield (%)
$Me(CH_2)_5CH{=}CH$ (*trans*)	$Me(CH_2)_5CH{=}CHCOOMe$ (*trans*)	91
$Me_3CCH{=}CH$ (*trans*)	$Me_3CCH{=}CHCOOMe$ (*trans*)	90
PhCH=CH (*trans*)	PhCH=CHCOOMe (*trans*)	76
$MeOCH_2CH{=}CH$ (*trans*)	$MeOCH_2CH{=}CHCOOMe$ (*trans*)	61
$MeOOC(CH_2)_8CH{=}CH$ (*trans*)	$MeOOC(CH_2)_8CH{=}CHCOOMe$ (*trans*)	72
		88
Ph	PhCOOMe	Trace
$PhCH_2$	$PhCH_2COOMe$	Trace

TABLE 100. Palladium dispersion catalysis in alkoxycarbonylation of olefins[2148]

Olefin	Alcohol	Catalyst	Salt	Ratio cat:salt	Product	Yield (%)
$Me(CH_2)_3CH{=}CH_2$	EtOH[a]	$PdCl_2(PPh_3)_2$	$Et_4\overset{+}{N}SnCl_3^-$	1:10	$Me(CH_2)_5COOEt$	51
$Me(CH_2)_5CH{=}CH_2$	EtOH[b]	$PdCl_2(PPh_3)_2$	$Me_4\overset{+}{N}SnCl_3^-$	1:5	$Me(CH_2)_7COOEt$	3.2[c]
$Me(CH_2)_5CH{=}CH_2$	EtOH[b]	$PdCl_2(PPh_3)_2$	$Et_4\overset{+}{N}SnCl_3^-$	1:10	$Me(CH_2)_7COOEt$	71.6[c]
$Me(CH_2)_5CH{=}CH_2$	EtOH[b]	$PdCl_2(PPh_3)_2$	$(n\text{-}Bu)_4\overset{+}{N}SnCl_3^-$	1:10	$Me(CH_2)_7COOEt$	49.6[c]
$Me(CH_2)_5CH{=}CH_2$	EtOH[b]	$PdCl_2(PPh_3)_2$	$(n\text{-}C_7H_{15})_4\overset{+}{N}SnCl_3^-$	1:5	$Me(CH_2)_7COOEt$	11.0[c]
$Me(CH_2)_5CH{=}CH_2$	EtOH[b]	$PdCl_2(PPh_3)_2$	$Me_3\overset{+}{N}PhSnCl_3^-$	1:10	$Me(CH_2)_7COOEt$	5.18[c]
$Me(CH_2)_5CH{=}CH_2$	EtOH[b]	$PdCl_2(PPh_3)_2$	$ClCH_2\overset{+}{P}Ph_3SnCl_3^-$	1:5	$Me(CH_2)_7COOEt$	58.5[c]
$Me(CH_2)_5CH{=}CH_2$	EtOH[b]	$PdCl_2(PPh_3)_2$	$Ph_4\overset{+}{A}sSnCl_3^-$	1:5	$Me(CH_2)_7COOEt$	24.4[c]
$Me(CH_2)_5CH{=}CH_2$	EtOH[b]	$PdCl_2[P(C_6H_5Me\text{-}p)]_2$	$Et_4\overset{+}{N}SnCl_3^-$	1:10	$Me(CH_2)_7COOEt$	74.4[c]
$Me(CH_2)_5CH{=}CH_2$	EtOH[b]	$PdCl_2(AsPh_3)_2$	$Et_4\overset{+}{N}SnCl_3^-$	1:10	$Me(CH_2)_7COOEt$	1.5[c]
$Me(CH_2)_5CH{=}CH_2$	EtOH[b]	$PdCl_2(PPh_3)_2$	$Et_4\overset{+}{N}SnCl_3^-$	1:25	$Me(CH_2)_7COOEt$	21.0[c]
$Me(CH_2)_5CH{=}CH_2$	EtOH[b]	$PdCl_2(PPh_3)_2$	$(Et_4\overset{+}{N}SnCl_3^-)\cdot PPh_3$	1:10:2	$Me(CH_2)_7COOEt$	6.9[c]
$Me(CH_2)_5CH{=}CH_2$	EtOH[b]	$PdCl_2(PPh_3)_2$	$(Et_4\overset{+}{N}SnCl_3^-)\cdot LiCl$[d]	1:10:33	$Me(CH_2)_7COOEt$	28.0[c]
$Me(CH_2)_5CH{=}CH_2$	EtOH[b]	$PdCl_2$	$Et_4\overset{+}{N}SnCl_3^-$	1:10	$Me(CH_2)_7COOEt$	Trace[c]
$Me(CH_2)_5CH{=}CH_2$	EtOH[b]	$PdCl_2(PPh_3)_2$	$Et_4\overset{+}{N}SnCl_3^-$	1:10	$Me(CH_2)_7COOEt$	Trace[c]
$Me(CH_2)_5CH{=}CH_2$	EtOH[b]	$PdCl_2(AsPh_3)_2$	$Et_4\overset{+}{N}SnCl_3^-$	1:10	$Me(CH_2)_7COOEt$	Trace[c]

$Me(CH_2)_5CH{=}CH_2$	EtOH[b]	K_2PtCl_4	$Et_4\overset{+}{N}SnCl_3^-$	1:10	$Me(CH_2)_7COOEt$	Trace[c]
$Me(CH_2)_5CH{=}CH_2$	EtOH[a]	$PdCl_2(PPh_3)_2$	$Et_4\overset{+}{N}SnCl_3^-$	1:10	$Me(CH_2)_7COOEt$	62
$Me(CH_2)_{11}CH{=}CH_2$	EtOH[a]	$PdCl_2(PPh_3)_2$	$Et_4\overset{+}{N}SnCl_3^-$	1:10	$Me(CH_2)_7COOEt$	64
$Me_3CCH{=}CH_2$	EtOH[a]	$PdCl_2(PPh_3)_2$	$Et_4\overset{+}{N}SnCl_3^-$	1:10	$Me_3CCH_2CH_2COOEt$	36
$Me_3CCH_2CMe{=}CH_2$	EtOH[a]	$PdCl_2(PPh_3)_2$	$Et_4\overset{+}{N}SnCl_3^-$	1:10	$Me_3CCH_2CHMeCH_2COOEt$	23
	EtOH[a]	$PdCl_2(PPh_3)_2$	$Et_4\overset{+}{N}SnCl_3^-$	1:10		42[e]
n-$BuCH{=}CHMe$[f]	EtOH[a,f]	$PdCl_2(PPh_3)_2$	$Et_4\overset{+}{N}SnCl_3^-$	1:10	*n*-PenCHMeCOOEt + *n*-$C_7H_{15}COOEt$	41
n-$PenCH{=}CH_2$[f,g]	EtOH[a,f]	$PdCl_2(PPh_3)_2$	$Et_4\overset{+}{N}SnCl_3^-$	1:10	*n*-$PenC(COOEt){=}CH_2$ + *n*-$PenCH{=}CHCOOEt$	39
n-$HexCH{=}CH_2$	$ClCH_2CH_2OH$[a]	$PdCl_2(PPh_3)_2$	$Et_4\overset{+}{N}SnCl_3^-$	1:10	*n*-$C_8H_{17}COOCH_2CH_2Cl$	21
n-$HexCH{=}CH_2$	Me_2CHOH[a]	$PdCl_2(PPh_3)_2$	$Et_4\overset{+}{N}SnCl_3^-$	1:10	*n*-$C_8H_{17}COOCHMe_2$	46
n-$HexCH{=}CH_2$	*n*-HexOH[a]	$PdCl_2(PPh_3)_2$	$Et_4\overset{+}{N}SnCl_3^-$	1:10	*n*-$C_8H_{17}COOHex$-*n*	57
n-$HexCH{=}CH_2$	C_6H_5OH[a]	$PdCl_2(PPh_3)_2$	$Et_4\overset{+}{N}SnCl_3^-$	1:10	*n*-$C_8H_{17}COOPh$	14

[a] Experimental conditions (alkene):((EtOH):(Pd) = 100:200:1; 100 atm CO; 85 °C, 8 h.
[b] Experimental conditions (1-C_8H_{16}):(EtOH):(Pd) = 100:100:1; 100 atm CO; 80 °C, 8 h.
[c] Other products include ethyl 2-methyloctanoate and ethyl 2-ethylheptanoate but yields were not reported.
[d] Initially (1-C_8H_{16}):(Pd) = 60:1.
[e] Some ethyl 3-methylcyclohexanecarboxylate was formed as a minor product.
[f] Initially (alkene):(Pd) = 50:1.
[g] Reaction time was 4 h.

TABLE 101. Palladium complex catalysts in alkoxycarbonylation of acetylenes.[2151]

Alkyne	Alcohol	Catalyst	Pressure CO (atm)	Temp. (°C)	Time (h)	Product	Yield[a] (mole %)
n-PenC≡CH	MeOH	$(Ph_3P)_2PdCl_2$–$SnCl_2$	136	70	2	*n*-PenCH=CHCOOMe	89[49]
n-PenC≡CH	MeOH	$(Ph_3P)_2PdCl_2$–$SnCl_2$[b]	240	80	3–6	*n*-PenCH=CHCOOMe	49[c]
n-PenC≡CH	MeOH	$(Ph_3P)_2PdCl_2$–$SnCl_2$[b]	240	80	3–6	*n*-PenCH=CHCOOMe	3[c]
n-PenC≡CH	MeOH	$(Ph_3P)_2PdCl_2$[b]	240	80	3–6	*n*-PenCH=CHCOOMe	16[c]
n-PenC≡CH	MeOH	$(Me_2C_6H_3P)_2PdCl_2$–$SnCl_2$[b]	240	80	3–6	*n*-PenCH=CHCOOMe	53[c]
n-PenC≡CH	MeOH	$(p\text{-}Tol_3P)_2PdCl_2$–$SnCl_2$	1	22	3–4	*n*-PenCH=CHCOOMe	64[93]
n-PenC≡CH	MeOH	$(p\text{-}Tol_3P)_2PdCl_2$–$SnCl_2$	70	22	3–4	*n*-PenCH=CHCOOMe	89[78]
n-PenC≡CH	MeOH	$(p\text{-}Tol_3P)_2PdCl_2$–$SnCl_2$	136	22	3–4	*n*-PenCH=CHCOOMe	82[68]
n-PenC≡CH	MeOH	$(p\text{-}Tol_3P)_2PdCl_2$–$SnCl_2$[b]	240	80	3–6	*n*-PenCH=CHCOOMe	43[c]
n-PenC≡CH	MeOH	$(o\text{-}Tol_3P)_2PdCl_2$–$SnCl_2$[b]	240	80	3–6	*n*-PenCH=CHCOOMe	Trace[c]
n-PenC≡CH	MeOH	$(p\text{-}An_3P)_2PdCl_2$–$SnCl_2$	1	22	3–4	*n*-PenCH=CHCOOMe	24[97]
n-PenC≡CH	MeOH	$(p\text{-}Tol_3P)_2PdCl_2$–$SnCl_2$[b]	240	80	3–6	*n*-PenCH=CHCOOMe	30[c]
n-PenC≡CH	MeOH	$[(p\text{-}ClC_6H_4)_3P]_2PdCl_2$–$SnCl_2$[b]	240	80	3–6	*n*-PenCH=CHCOOMe	7[c]
n-PenC≡CH	MeOH	$[(PhO)_3P]_2PdCl_2$–$SnCl_2$[b]	240	80	3–6	*n*-PenCH=CHCOOMe	Trace[c]
n-PenC≡CH	MeOH	$(c\text{-}Hex_3P)_2PdCl_2$–$SnCl_2$[b]	240	80	3–6	*n*-PenCH=CHCOOMe	Trace[c]
n-PenC≡CH	MeOH	$[(n\text{-}Bu)_3P]_2PdCl_2$–$SnCl_2$[b]	240	80	3–6	*n*-PenCH=CHCOOMe	9[c]
n-PenC≡CH	MeOH	$(Ph_3As)_2PtCl_2$–$SnCl_2$[b]	240	80	3–6	*n*-PenCH=CHCOOMe	21[c]
n-PenC≡CH	MeOH	K_2PtCl_6–$SnCl_2$[b]	240	80	3–6	*n*-PenCH=CHCOOMe	13[c]
$Me_2CHC{\equiv}CH$	*n*-PrOH	$(p\text{-}Tol_3P)_2PdCl_2$–$SnCl_2$	136	22	3–4	$Me_2CHCH{=}CHCOOPr\text{-}n$	56[72]
$Me_3CC{\equiv}CH$	*n*-PrOH	$(p\text{-}Tol_3P)_2PdCl_2$–$SnCl_2$	136	22	3–4	$Me_3CCH{=}CHCOOPr\text{-}n$	30[99]
PhC≡CH	MeOH	$(p\text{-}Tol_3P)_2PdCl_2$–$SnCl_2$	136	22	3–4	PhCH=CHCOOMe	10[27]
PhC≡CPh	MeOH	$(p\text{-}Tol_3P)_2PdCl_2$–$SnCl_2$	136	22	3–4	PhCH=CPhCOOMe	50[47]

[a]Yield (mole%) based upon alkyne converted. The selectivity in mole% which is the linear ester:total linear + branched ester is reported in brackets.
[b]Methyl isobutyl ketone also present.
[c]Isolated % yield.

In another report[2152] the palladium chloride catalyzed methoxycarbonylation of (*E*)-alkenylpentafluorosilicates is presented. Although these reactions appear to be methoxycarbonylations of olefins and not acetylenes, because the silicates used as substrates are prepared from acetylenes (equation 1118), they are included in this section.

b. Of mono- and dihalides. Aliphatic halides have been converted into esters by alkoxycarbonylation reactions catalyzed by a variety of metal catalysts. Reaction of aliphatic halides with carbon monoxide and alcohol in the presence of a metal cobalt carbonyl complex on an ion-exchange resin containing an amine group produces[2153] the corresponding acid esters in good yields (equations 1119 and 1120).

$$R^1X + CO + R^2OH \xrightarrow[\text{ion exchange resin}]{MCo(CO)_n} R^1COOR^2 \qquad (1119)$$

R = substituted or unsubstituted hydrocarbon
Y = Cl, Br, I
M = Na, K, Li, Co, Mn, Fe, etc.
n = valence of M

ion exchange resin = molecules containing $CH_2\overset{+}{N}Me_3\bar{X}$; $CH_2\overset{+}{N}(CH_2CH_2OH)Me_2\bar{X}$ or CH_2NMe_2 (example, Amberlyst A26)

$$PhCH_2Cl + CO + EtOH \xrightarrow[47\,^\circ C,\ \text{Amberlyst A26}]{K_2CO_3,\ NaCo(CO)_4,} PhCH_2COOEt \qquad (1120)$$

65%

Rhodium chloride catalysts have also been reported[2154,2155] to catalyze the alkoxycarbonylation of aliphatic halides with carbon monoxide and alcohols[2154] (equations 1121 and 1122) or alkoxymetals[2155] (equation 1123).

$$PhCH_2Cl + CO + MeOH \xrightarrow[NaOMe,\ \text{heat}]{RhCl_3,\ HI} PhCH_2COOMe \qquad (1121)$$

$$EtOOCCH_2Cl + CO + EtOH \xrightarrow[NaOMe,\ \text{heat}]{RhCl_3,\ HI} CH_2(COOEt)_2 \qquad (1122)$$

$$R^1X + CO + M(OR^2)_n \xrightarrow[\text{rhodium chloride dimer}]{\text{1,5-hexadiene-}} R^1COOR^2 \qquad (1123)$$

R^1 = substituted or unsubstituted hydrocarbon radical
X = Cl, Br, I
M = B, Si, Al, Ti, Zr
n = valence of M

Example:

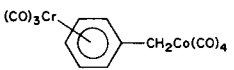
$$PhCH_2Br + CO + Al(OEt)_3 \xrightarrow[\text{rhodium chloride dimer}]{\text{1,5-hexadiene-}} PhCH_2COOEt$$

With the aromatic and heterocyclic halide series alkoxycarbonylation was accomplished using[2156] alkylcobalt carbonyl complexes, either preformed or generated *in situ*, in the presence of carbon monoxide at one atmosphere, a base (alkoxide, sodium hydroxide or potassium carbonate) and an aliphatic alcohol or halide (equation 1124). Table 102 lists the results obtained with various aromatic halides, catalysts, bases and alcohols or halides.

$$ArX + CO(1\ atm) + ROH \xrightarrow[R'Y + Co(CO)_4^{\ominus},\ \text{base, } 25\,^\circ C]{ECH_2Co(CO)_4\ \text{or}} ArCOOR \qquad (1124)$$

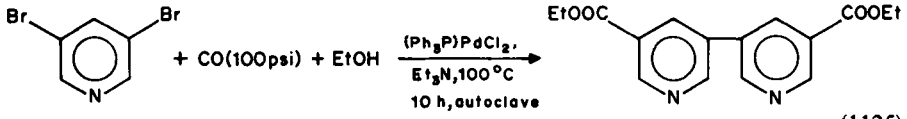
TABLE 102. Alkoxycarbonylation of aromatic and heteroaromatic halides using cobalt carbonyl complexes as catalysts[2156]

Halide	R'Y	Catalyst	Temp. (°C)	ROH	Base	Product	Yield (%)
PhBr	MeOH	$EtOOCCH_2Co(CO)_4$	25	MeOH	NaOMe	PhCOOMe	86
PhBr	MeOH	$FCH_2Co(CO)_4$	25	MeOH	NaOMe	PhCOOMe	66
PhBr	n-$C_8H_{17}Br$	$Co(CO)_4^-$	60	MeOH	K_2CO_3	PhCOOMe	97
PhBr	$ClCH_2COOMe$	$Co(CO)_4^-$	60	MeOH	K_2CO_3	PhCOOMe	90
PhBr	p-$ClC_6H_4CH_2Cl$	$Co(CO)_4^-$	35	MeOH	K_2CO_3	PhCOOMe	70
p-TolBr	MeOH	$EtOOCCH_2Co(CO)_4$	25	MeOH	NaOMe	p-TolCOOMe	12
p-TolBr	$ClCH_2COOMe$	$Co(CO)_4^-$	60	MeOH	K_2CO_3	p-TolCOOMe	70
p-AnBr	$ClCH_2COOMe$	$Co(CO)_4^-$	60	MeOH	K_2CO_3	p-AnCOOMe	73
m-AnBr	MeOH	$EtOOCCH_2Co(CO)_4$	25	MeOH	NaOMe	m-AnCOOMe	51
p-ClC_6H_4Br	MeOH	$EtOOCCH_2Co(CO)_4$	25	MeOH	NaOMe	p-ClC_6H_4COOMe	77
p-ClC_6H_4Br	$ClCH_2COOMe$	$Co(CO)_4^-$	60	MeOH	K_2CO_3	p-ClC_6H_4COOMe +	80
						p-$MeOOCC_6H_4COOMe$	1.5
m-ClC_6H_4Br	MeOH	$MeOOCCH_2Co(CO)_4$	25	MeOH	NaOMe	m-ClC_6H_4COOMe	76
m-ClC_6H_4Br	MeOH	$EtOOCCH_2Co(CO)_4$	25	MeOH	NaOMe	m-ClC_6H_4COOMe	78
m-ClC_6H_4Br	MeOH	$NCCH_2Co(CO)_4$	25	MeOH	NaOMe	m-ClC_6H_4COOMe	43
o-ClC_6H_4Br	MeOH	$EtOOCCH_2Co(CO)_4$	25	MeOH	NaOMe	o-ClC_6H_4COOMe +	45
						o-$MeOOCC_6H_4COOMe$	6.5

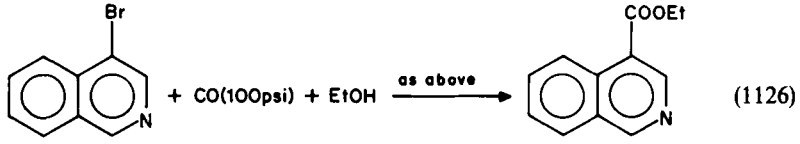
p-BrC_6H_4Br	MeOH	$EtOOCCH_2Co(CO)_4$	25	MeOH	NaOMe	*p*-$MeOOCC_6H_4COOMe$	77
p-BrC_6H_4Br	MeOH	$Co(CO)_4^-$	60	MeOH	K_2CO_3	*p*-$MeOOCC_6H_4COOMe$	98
1-NaphCl	MeOH	$EtOOCCH_2Co(CO)_4$	0	MeOH	NaOMe	1-NaphCOOMe	16
1-NaphCl	MeOH	$EtOOCCH_2Co(CO)_4$	25	MeOH	NaOMe	1-NaphCOOMe	67
1-NaphCl	EtOH	$EtOOCCH_2Co(CO)_4$	25	EtOH	NaOEt	1-NaphCOOEt	53
1-NaphCl	*i*-PrOH	$EtOOCCH_2Co(CO)_4$	25	*i*-PrOH	NaOPr-*i*	1-NaphCOOPr-*i*	20
1-NaphCl	MeOH	$FCH_2Co(CO)_4$	25	MeOH	NaOMe	1-NaphCOOMe	52
1-NaphCl	EtOH	$FCH_2Co(CO)_4$	25	EtOH	NaOEt	1-NaphCOOEt	42
1-NaphCl	MeOH		25	MeOH	NaOMe	1-NaphCOOMe	22
1-NaphCl	$ClCH_2COOMe$	$Co(CO)_4^-$	60	MeOH	K_2CO_3	1-NaphCOOMe	82
1-NaphCl	MeOH	$EtOOCCH_2Co(CO)_4$	25	MeOH	NaOMe	1-NaphCOOMe	72
1-NaphCl	MeOH	$EtOOCCH_2Co(CO)_4$	25	MeOH	K_2CO_3	1-NaphCOOMe	33
1-NaphCl	$ClCH_2COOMe$	$Co(CO)_4^-$	60	MeOH	K_2CO_3	1-NaphCOOMe	91
2-ThiCl	MeOH	$EtOOCCH_2Co(CO)_4$	25	MeOH	NaOMe	2-ThiCOOMe	78
2-ThiCl	MeI	$Co(CO)_4^-$	35	MeOH	K_2CO_3	2-ThiCOOMe	60
2-ThiCl	$PhCH_2Cl$	$Co(CO)_4^-$	35	MeOH	K_2CO_3	2-ThiCOOMe	72
2-ThiCl	$ClCH_2COOMe$	$Co(CO)_4^-$	60	MeOH	K_2CO_3	2-ThiCOOMe	98
2-ThiBr	$ClCH_2COOMe$	$Co(CO)_4^-$	60	MeOH	K_2CO_3	2-ThiCOOMe	95
3-FuBr	MeOH	$EtOOCCH_2Co(CO)_4$	25	MeOH	NaOMe	3-FuCOOMe	45
3-FuBr	$ClCH_2COOMe$	$Co(CO)_4^-$	60	MeOH	K_2CO_3	3-FuCOOMe	93
3-PyrBr	MeOH	$EtOOCCH_2Co(CO)_4$	25	MeOH	NaOMe	3-PyrCOOMe	57

X = Cl or Br (Br better leaving group than Cl)
R = Me, Et, *i*-Pr
Y = OH or X (MeOH best reagent and solvent)
base = alkoxides, NaOH, K_2CO_3 (NaOR best bases)
E = electron-withdrawing group (the presence of an electron-withdrawing group on the aromatic ring strongly favors the reaction)

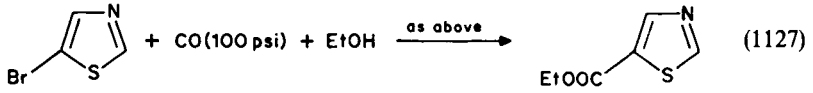
Halogenated heterocycles can also be alkoxycarbonylated using[2157] triphenylphosphine palladium dichloride in the presence of triethylamine (equations 1125, 1126 and 1127).



(1125)

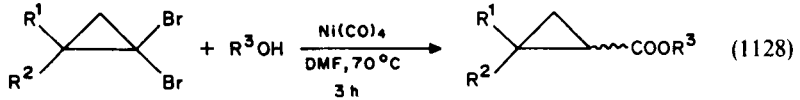


(1126)



(1127)

Treatment[2158] of *gem*-dibromocyclopropanes with alcohols in the presence of nickel tetracarbonyl produces the corresponding cyclopropanecarboxylates (equation 1128). However, this reaction is completely suppressed[2158] under a pressure of carbon monoxide gas, and does not proceed if monobromocyclopropanes are used[2158] as the substrates; but, if 1,1-dibromo-2-chlorocyclopropanes or related compounds are used as the substrates[2159,2160], ring-opening occurs during alkoxycarbonylation producing β,γ-unsaturated carboxylic and, in some cases, dicarboxylic acid esters (equation 1129). The mechanism proposed[2159,2160] for this conversion involves the initial reaction of the nickel tetracarbonyl with the alcohol to produce the nickel enolate complex, which then reacts

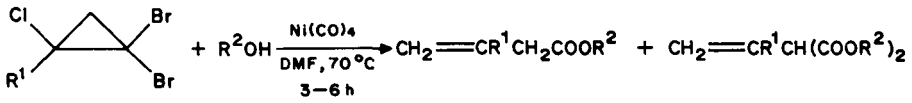


(1128)

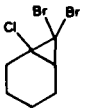
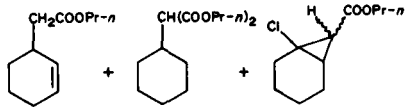
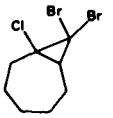
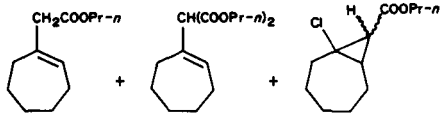
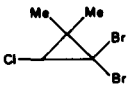
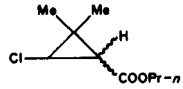
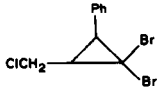
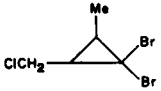
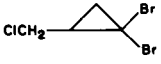
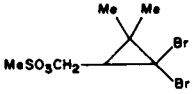
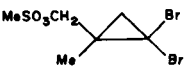
R^1	R^2	R^3	Yield (%)
Ph	H	*n*-Pr	62[a]
Ph	H	Ph	57
Ph	H	*m*-ClC_6H_4	56
Me	MeCOO	*n*-Pr	75
Me	CN	*n*-Pr	51

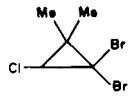
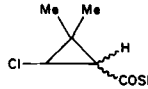
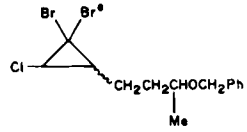
[a] *trans:cis* ratio 34:66.

with the dibromide to form a complex; displacement by attack of the alkoxycarbonyl group on the complex followed by either decarboxylation or hydride transfer produces the β,γ-unsaturated esters.



(1129)

Substrate	Alcohol	Products (ratio)	Yield (%)
	*n*-PrOH		
		(61:29:10[a])[b]	31
		(35:61:4[a])[c,d]	46
		(49:45:6[a])[c]	57
	*n*-PrOH		
		(43:40:17[a])[c]	80
	*n*-PrOH	$Me_2C{=}CHCH_2COOPr\text{-}n$ + $Me_2C{=}CHCH(COOPr\text{-}n)_2$ + 	
		(52:48:1[e])[c]	33
	*n*-PrOH	$CH_2{=}CH{-}\underset{\displaystyle Ph}{\underset{\vert}{CH}}{-}CH_2COOPr\text{-}n$	73
	*n*-PrOH	$CH_2{=}CH{-}\underset{\displaystyle Me}{\underset{\vert}{CH}}{-}CH_2COOPr\text{-}n$	63
	*n*-PrOH	$CH_2{=}CHCH_2CH_2COOPr\text{-}n$	61
	*n*-PrOH	$CH_2{=}CHC(Me)_2CH_2COOPr\text{-}n$	80
	*n*-PrOH	$CH_2{=}\underset{\displaystyle Me}{\underset{\vert}{C}}CH_2CH_2COOPr\text{-}n$	20

Substrate	Alcohol	Products (ratio)	Yield (%)
	PhSH	$Me_2C{=}CHCH_2COSPh$ + $Me_2C{=}CHCH(COSPh)_2$ +  (58:1:42[e])[c]	19
	*n*-PrOH	*n*-$PrOOCCH_2CH{=}CHCH_2$—CH_2CHOCH_2Ph[e] | Me	45

[a] An *endo* and *exo* mixture.
[b] Using 1 equivalent of alcohol.
[c] Using 2.2 equivalents of alcohol.
[d] Reaction time of 3 h.
[e] A *cis–trans* mixture.

At least one report[2161] describes the methoxycarbonylation of a dihalide and involves the reaction of 1,2-dichloropropane with carbon monoxide and methanol in the presence of 2,6-di(*t*-butyl)-*p*-cresol as a radical inhibitor and palladium on alumina as a catalyst to produce the α-unsaturated ester methyl methacrylate (equation 1130).

$$MeCHClCH_2Cl + CO + MeOH \xrightarrow[\substack{Pd/Al_2O_3,\,C_6H_6,\,240\,^\circ C\\ 1.75\,h}]{\text{2,6-di(}t\text{-butyl)-}p\text{-cresol}} CH_2{=}CMeCOOMe \quad (1130)$$

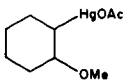
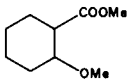
c. Of organometallic compounds. Alkoxycarbonylation of Grignard reagents has been accomplished[2162] using iron pentacarbonyl followed by treatment with iodine and alcohols (equation 1131). The mechanism[2162] for these conversions involves initial reaction of the iron pentacarbonyl with the Grignard reagent to form acyltetracarbonylferrate magnesium bromide salts, which then react with the alcohol (equation 1132) in the presence of iodine.

$$R^1MgBr + Fe(CO)_5 \xrightarrow[\text{2. } I_2, R^2OH, \text{stir 1 h}]{\text{1. THF, } N_2\text{, stir 1 h}} R^1COOR^2 \quad (1131)$$

R^1	R^2OH	Product	Yield (%)
Ph	$PhCH_2OH$	$PhCOOCH_2Ph$	78
Ph	EtOH	PhCOOEt	82
Ph	PhOH	PhCOOPh	63
n-Bu	EtOH	*n*-BuCOOEt	89
n-Bu	$PhCH_2OH$	*n*-$BuCOOCH_2Ph$	73
p-Tol	*n*-PrOH	*p*-TolCOOPr-*n*	71

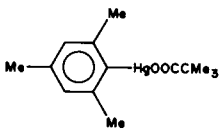
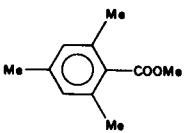
$$R^1MgBr + Fe(CO)_5 \rightarrow [R^1\overset{\overset{O}{\|}}{C}{-}Fe(CO)_4]^{\ominus}[MgBr]^{\oplus} \xrightarrow[I_2]{R^2OH} R^1COOR^2 \quad (1132)$$

TABLE 103. Methoxycarbonylation of organomercury compounds[2163]

Organomercury compounds	Catalyst	Temp (°C)	Time (h)	Pressure CO (psig)	Product	Yield (%)
EtHgOAc	$(Ph_3P)_3RhCl$	65–100	0.5–40	100–500	EtCOOMe	66
n-HexHgOAc	$(Ph_3P)_3RhCl$	65	6	100	*n*-HexCOOMe	63
n-HexHgBr	$(Ph_3P)_3RhCl$	75	72	70	*n*-HexCOOMe	72
n-$C_{12}H_{25}HgOAc$	$(Ph_3P)_3RhCl$	65–100	0.5–40	100–500	*n*-$C_{12}H_{25}COOMe$	48
n-BuCH(OMe)HgOAc	$(Ph_3P)_3RhCl$	65–100	0.5–40	100–500	*n*-BuCH(OMe)COOMe	28
$AcOCH_2CH_2HgOAc$	$(Ph_3P)_3RhCl$	65–100	0.5–40	100–500	$AcOCH_2CH_2COOMe$	31
	$(Ph_3P)_3RhCl$	65–100	0.5–40	100–500		21
$CH_2=CHHgOAc$	$(Ph_3P)_3PdCl$	75–100	1–3	50–100	$CH_2=CHCOOMe$	74
$CH_2=C(Me)HgOAc$	$(Ph_3P)_3PdCl$	75–100	1–3	50–100	$CH_2=C(Me)COOMe$	31
$Ph_2C=CHHgOAc$	$(Ph_3P)_3PdCl$	75–100	1–3	50–100	$Ph_2C=CHCOOMe$	36
$CH_2=CHCH_2HgOAc$	$(Ph_3P)_3RhCl$	65–100	0.5–40	100–500	$CH_2=CHCH_2COOMe$	35
$PhCH(OMe)CH_2HgI$	$(Ph_3P)_3RhCl$	65	100	50	$PhCH(OMe)CH_2COOMe$	44
PhHgCl	$(Ph_3P)_2PdCl_2$	75	0.5	100	PhCOOMe	26
$PhHgNO_3$	$(Ph_3P)_2PdCl_2$	75	0.5	100	PhCOOMe	56
PhHgOAc	$(Ph_3P)_2PdCl_2$	75–100	1–3	50–100	PhCOOMe	83
$PhHgOOCCF_3$	$(Ph_3P)_2PdCl_2$	95	1	70	PhCOOMe	69

(continued)

TABLE 103 (*continued*)

Organomercury compounds	Catalyst	Temp (°C)	Time (h)	Pressure CO (psig)	Product	Yield (%)
$PhHgOOCCF_3$	Na_2PdCl_4	75–100	0.4–6	75–150	PhCOOMe	7[a]
$PhHgOOCCF_3$	$PdCl_2$	75–100	0.4–6	75–100	PhCOOMe	24[a]
$PhHgOOCCF_3$	$PdCl_2 + Ph_3P$	75–150	0.4–6	75–100	PhCOOMe	72[a]
$PhHgOOCCF_3$	$PdCl_2 + A$[b]	75–150	0.4–6	75–100	PhCOOMe	21[a]
$PhHgOOCCF_3$	$PdCl_2 + B$[c]	75–150	0.4–6	75–100	PhCOOMe	60[a]
$PhHgOOCCF_3$	$[(n\text{-}Bu)_2P]_2PdCl_2$	75–150	0.4–6	75–100	PhCOOMe	69[a]
$PhHgOOCCF_3$	$(Ph_3P)_2PtCl_2$	75–150	0.4–6	75–100	PhCOOMe	35[a]
$PhHgOOCCF_3$	$(Ph_3P)_3RhCl$	75–150	0.4–6	75–100	PhCOOMe	56[a]
$PhHgOOCCF_3$	$(Ph_3P)_4Pd$	75–150	0.4–6	75–100	PhCOOMe	50[a]
$PhHgOOCCF_3$	$(Ph_3P)_4Pt$	75–150	0.4–6	75–100	PhCOOMe	34[a]
	$(Ph_3P)_2PdCl_2$	75	5	100		20

[a]These yields reported as weight percents.
[b]A = Bis(1,2-diphenylphosphino)ethane.
[c]B = Tri(isopropyl)phosphite.

In addition to the substituted vinyl mercuric chlorides discussed in Section III.D.1.a, other organomercury compounds also react with carbon monoxide in alcoholic media to produce carboxylic acid esters with catalysis[2163] by homogeneous group 9 and 10 metal complexes (equation 1133). The results of this approach to the preparation of methyl esters of carboxylic acids are reported in Table 103. Mercuration of substituted benzenes leads to an isomer distribution in the intermediate, which upon methoxycarbonylation leads to a similar isomer distribution in the ester obtained as shown[2163] in equation 1134.

$$R^1HgX + CO + R^2OH \xrightarrow[\substack{50\text{–}150\,^\circ C\\ 0.5\text{–}24\,h\\ (1\text{–}50\,atm)}]{\text{catalyst}} R^1COOR^2 + Hg + HX \qquad (1133)$$

R^1	R^2OH	Catalyst
Aryl	Water	$(Ph_3P)_2PdCl_2$
Alkyl	Alcohols	$(Ph_3P)_4Pd$
Allyl	Phenols	$Pd + Ph_3P$
Vinyl	Polyols	$(Ph_3P)_3RhCl$
β-Oxyalkyl	Acids	$(Ph_3P)_4Pd$

$$ArH + HgX_2 \longrightarrow ArHgX + CO(50\text{–}100\,psig) + MeOH \xrightarrow[\substack{75\text{–}100\,^\circ C\\ 1\text{–}3\,h}]{(Ph_3P)_2PdCl_2}$$

ArCOOMe (*ortho*, *meta* and *para* isomers) (1134)

Aromatic	X	Yield (%)	isomer distribution (locant) ortho	meta	para
MeC_6H_4	CF_3COO	88	47	25	28
EtC_6H_4	CF_3COO	89	35	8	57
t-BuC_6H_4	CF_3COO	75	0	28	72
o-$Me_2C_6H_3$	OAc	85	15(3)	0	85(4)
m-$Me_2C_6H_3$	OAc	64	80(4)	0	20(5)
p-$Me_2C_6H_3$	OAc	84			
2,4,6-$Me_3C_6H_2$	CF_3COO	30			
1,2,4-$Me_3C_6H_2$	OAc	69	92%(2,4,5-), 6%(2,3,5-), 2%(2,3,6-trimethyl)		
PhC_6H_4	CF_3COO	60			100(4)
Naph	CF_3COO	60	30(α)	70(β)	
ClC_6H_4	CF_3COO	75	14	0	86
An	OAc	70	16	0	84
An	CF_3COO	79	86	0	14
$MeOOCC_6H_4$	CF_3COO	68	70	30	0
p-$(MeOOC)_2C_6H_3$	CF_3COO	30	100(3)	0	0
$H_2NC_6H_4$	OAc	10	2	0	98
$Me_2NC_6H_4$	OAc	47	0	0	> 98

Aromatic	X	Yield (%)	isomer distribution (locant) ortho	meta	para
$MeCONHC_6H_4$	OAc	78	0	0	>98
PhC_6H_4	CF_3COO	67[a]	0	0	100(4,4')
o-$Me_2C_6H_3$	CF_3COO	67[a]	dimethyl 4,5-dimethylphthalate,		94
m-$Me_2C_6H_3$	CF_3COO	30[a]	dimethyl 4,6-dimethylisophthalate,		72
p-$Me_2C_6H_3$	CF_3COO	33[a]	dimethyl 2,5-dimethylterephthalate,		30

[a] Dimercuration/dimethoxycarbonylation.

d. Of alcohols. Both alcohols[2164] and alkoxides[2165] have been used as starting materials in the preparation of carboxylic acid esters by alkoxycarbonylation reactions.

By reaction[2164] of methanol with a 2:1 gaseous mixture of hydrogen and carbon monoxide at 2000 psi in the presence of a cobalt–thallium catalyst which has been treated with 10% hydrogen sulfide, methyl acetate is obtained in addition to several other products (equation 1135). This reaction is interesting because the methanol acts as both the initial substrate and the alcohol in the methoxycarbonylation.

$$\underset{\substack{(2:1)\\2000\text{ psi}}}{MeOH + H_2 + CO} \xrightarrow[230\,^\circ C,\ 12.5\,h]{Co\text{–}Tl\text{ on alumina}} MeCOOMe + MeCH(OMe)_2 + EtOH + Me_2O + HCOOMe \qquad (1135)$$

Treatment[2165] of the sodium alkoxides of aliphatic alcohols with iron pentacarbonyl in tetrahydrofuran-*N*-methylpyrrolidone (THF–NMP) produces intermediate alkoxycarbonyltetracarbonyl ferrates, which upon reaction with alkyl halides afford the corresponding carboxylic acid esters (equation 1136). This reaction is very similar in both scope and mechanism to the reaction of Grignard reagents with iron pentacarbonyl and alcohols reported in Section III.D.1.c, with the exception that in this reaction the alkoxide which forms the ferrate intermediate produces the ester function of the product and not the acid function, as is the case with the Grignard reagent reaction.

$$R^1O^{\ominus}Na^{\oplus} + Fe(CO)_5 \xrightarrow[\substack{\text{stir 1 h, r.t.,}\\\text{under Ar}}]{THF\text{–}NMP} [R^1O\text{-}C(=O)Fe(CO)_4]^{\ominus}Na^{\oplus} \xrightarrow[\substack{\text{stir}\\24\,h}]{R^2X} R^2COOR^1 \qquad (1136)$$

R^1	R^2X	Solvent	Product	Yield (%)
i-Pr	EtI	THF–NMP	EtCOOPr-*i*	80
n-Bu	*n*-PrI	THF–NMP	*n*-PrCOOBu-*n*	62
n-Bu	EtI	THF–NMP	EtCOOBu-*n*	68
n-Bu	EtI	THF	EtCOOBu-*n*	30
$PhCH_2$	EtI	THF–NMP	$EtCOOCH_2Ph$	61
$PhCH_2$	EtI	THF	$EtCOOCH_2Ph$	20
Et	$BrCH_2COOEt$	THF–NMP	$CH_2(COOEt)_2$	48

e. Of sulfonium salts. Treatment[2166] of triarylsulfonium salts with carbon monoxide and alcohol in the presence of triarylphosphine and a zero-valent palladium or rhodium produces carboxylic acid ester by alkoxycarbonylation (equation 1137).

General reaction:

$$R^1{}_3S^{\oplus}X^{\ominus} + CO + R^2OH \xrightarrow[\text{metal cat.}]{Ar_3P,} R^1COOR^2 \qquad (1137)$$

R^1 = carbocyclic or heterocyclic aromatic moiety
X = weak acid anion
$R^2 = C_1$ to C_{12} alkyl
metal cat. = zero-valent Pd or Rh

Example:

$$p\text{-}Tol_3S^{\oplus}I^{\ominus} + CO + MeOH \xrightarrow[\substack{Ph_3P,\ Na_2CO_3,\\ \text{reflux, 2 h}}]{Pd(OAc)_2,} p\text{-}TolCOOMe \quad 82\%$$

7. Thiolation

The sulfur analog of the alkoxycarbonylation reactions presented in Sections III.D.1.a–e can be accomplished[2167] by reaction of phenacyl halides with elemental sulfur in the presence of triethylamine, followed by reaction with methyl iodide (equation 1138). The methyl esters of the α-oxodithiocarboxylic acids thus produced are obtained in yields ranging from 40 to 70%.

$$\underset{\underset{O}{\|}}{ArCCH_2X} \xrightarrow[\text{2. MeI}]{\text{1. S, } Et_3N\text{, aprotic solvent}} \underset{\underset{O}{\|}}{ArC}\!-\!\overset{\overset{S}{\|}}{C}\!-\!SMe \qquad (1138)$$

Ar = Ph, *p*-An, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-PhC_6H_4, 3,4-$(HO)_2C_6H_3$, β-Naph
X = Cl, Br
aprotic solvent = DMF, DMSO, HMPT

8. By addition of carboxylic acids to multiple bonds

Addition of carboxylic acids across an olefin double bond catalyzed by a variety of reagents can be used to generate carboxylic acid esters. The general reaction is illustrated in equation 1139 while the details of individual reactions are presented in Table 104. As can be seen from equation 1139, if unsymmetrical olefins are used in the reaction, isomeric products can be formed.

$$R^1COOH + R^2CH{=}CHR^3 \xrightarrow{\text{cat.}} R^1COOCHR^2CH_2R^3 + R^1COOCHR^3CH_2R^2 \qquad (1139)$$

An interesting modification of the approach described above which can be used for the preparation of perfluorocarboxylic acid esters is the addition[2172] of fluorinated acyl hypochlorites to olefins. Actually two methods may be used to produce esters by this

TABLE 104. Esters by addition of carboxylic acids to double bonds

Alkene	Acid	Catalyst	Temp. (°C)	Time (h)	Product	Yield (wt%)	Reference
$CH_2=CH_2$	MeCOOH	*a*	200	40	MeCOOEt	92.4	2168
$CH_2=CH_2$	MeCOOH	SiO_2-metal oxide[b]	—	—	MeCOOEt	—	2169
$MeCH=CH_2$	MeCOOH	*a*	200	10	MeCOOPr-*i* +	39.5	2168
					MeCOOPr-*n*	Trace	
$MeCH=CH_2$	MeCOOH	SiO_2-Metal oxide[b]	—	—	MeCOOPr-*i*	—	2169
n-$PrCH=CH_2$	MeCOOH	*a*	160	4	MeCOOCH(Me)Pr-*n* +	20.5	2168
					$MeCOOCHEt_2$	5.7	
n-$BuCH=CH_2$	MeCOOH	*a*	160	4	MeCOOCH(Me)Bu-*n* +	15.6	2168
					MeCOOCH(Et)Pr-*n*	6.3	
$Me_2CHCH_2CH=CH_2$	MeCOOH	*a*	160	4	$MeCOOCH(Me)CH_2CHMe_2$ +	7.8	2168
					$MeCOOCH(Et)CHMe_2$	1.5	
n-$PenCH=CH_2$	MeCOOH	*a*	160	4	MeCOOCH(Me)Pen-*n* +	12.1	2168
					MeCOOCH(Et)Bu-*n* +	3.3	
					$MeCOOCH(Pr\text{-}n)_2$	Trace	
n-$HexCH=CH_2$	MeCOOH	*a*	160	4	MeCOOCH(Me)Hex-*n* +	8.2	2168
					MeCOOCH(Et)Pen-*n* +	1.8	
					MeCOOCH(Pr-*n*)Bu-*n*	Trace	
n-$C_7H_{15}CH=CH_2$	MeCOOH	*a*	160	4	$MeCOOCH(Me)C_7H_{15}$-*n* +	8.6	2168
					$MeCOOCH(Et)C_6H_{13}$-*n* +	1.6	
					$MeCOOCH(Pr\text{-}n)C_5H_{11}$-*n* +	Trace	
					$MeCOOCH(Bu\text{-}n)_2$	Trace	
n-$C_8H_{17}CH=CH_2$	MeCOOH	*a*	160	4	$MeCOOCH(Me)C_8H_{17}$-*n* +	10.2	2168
					$MeCOOCH(Et)C_7H_{15}$-*n* +	2.2	
					$MeCOOCH(Pr\text{-}n)C_6H_{13}$-*n* +	Trace	
					$MeCOOCH(Bu\text{-}n)C_5H_{11}$-*n* +	Trace	
n-$C_8H_{17}CH=CH_2$	MeCOOH	Dealuminized zeolite	120	25	$MeCOOCH(Me)C_8H_{17}$-*n*	80.0[c]	2170
EtCH=CHMe (*trans*)	MeCOOH	*a*	160	4	MeCOOCH(Me)Pr-*n* +	15.4	2168
					$MeCOOCHEt_2$	6.0	

n-PrCH=CHMe	MeCOOH		*a*	160	4	MeCOOCH(Me)Bu-*n* + MeCOOCH(Et)Pr-*n*	9.5 3.6	2168
Cyclohexene	MeCOOH		*a*	160	4	MeCOOHex-*c*	13.0	2168
$Me_2C=CH_2$	MeCOOH		*a*	18	24	MeCOOBu-*t*	23.0	2168
$EtCMe=CH_2$	MeCOOH		*a*	18	24	$MeCOOC(Me)_2Et$	3.6	2168
n-PrCMe=CH_2	MeCOOH		*a*	18	24	$MeCOOC(Me)_2Pr$-*n*	5.3	2168
$Et_2C=CH_2$	MeCOOH		*a*	18	24	$MeCOOCH(Et)CHMe_2$	2.9	2168
n-PenCH=CH_2	HCOOH		*a*	80	12	HCOOCH(Me)Pen-*n* + HCOOCH(Et)Bu-*n*	75.3 Trace	2168
n-PenCH=CH_2	MeCOOH		*a*	160	4	MeCOOCH(Me)Pen-*n* + MeCOOCH(Et)Bu-*n*	15.6 6.3	2168
n-PenCH=CH_2	EtCOOH		*a*	160	4	EtCOOCH(Me)Pen-*n* + EtCOOCH(Et)Bu-*n*	11.9 6.3	2168
n-PenCH=CH_2	*n*-PrCOOH		*a*	160	4	*n*-PrCOOCH(Me)Pen-*n* + *n*-PrCOOCH(Et)Bu-*n*	11.7 5.7	2168
$CH_2=CHCN$	RCOOH[d]	$Cu(PPh_3)_2Cl_2$ or $Rh(PPh_3)_3Cl$		135	—	$RCOOCH_2CH_2CN$	—	2171
$CH_2=CHCN$	$HOOC(CH_2)_nCOOH$ $n = 0–4$	$Cu(PPh_3)_2Cl_2$ or $Rh(PPh_3)_3Cl$		135	—	$NC(CH_2)_2OOC(CH_2)_nCOO(CH_2)_2CN$ $n = 0–4$		—

[a]Ion-exchange sheet silicates, Al^{+3} ion-exchange montomorillonite.
[b]Metal oxide = Na_2O, Cr_2O_3, B_2O_3 or La_2O_3.
[c]Isolated % yield.
[d]R = Me, Et, *n*-Pr, CH=CHMe, *n*-C_7H_{15}.

approach: Method A (equation 1140) involves the initial preparation of the acyl hypochlorite by reaction of the sodium salt of the carboxylic acid with ClF under the conditions presented in equation 1140, followed by addition of the acyl hypochlorites thus prepared to the olefins (equation 1141). Method B is similar to Method A, except that it is a one-pot procedure (equation 1142). The results reported[2172] indicate that the addition is both regio- and stereospecific with respect to the olefins and led the authors[2172] to propose a concerted type of mechanism for this addition (equation 1143).

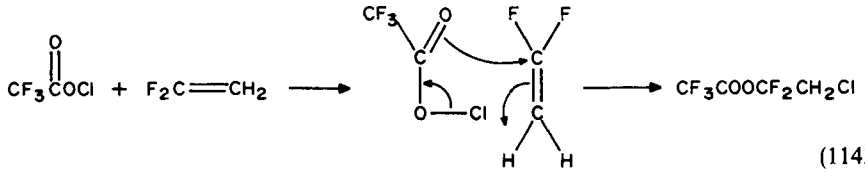
$$RCOO^{\ominus}Na^{\oplus} + ClF \xrightarrow[\text{2. Warm over 6 h to } -78\,^{\circ}C \text{ 3. Hold at } -78\,^{\circ}C \text{ for 18 h}]{\text{1. Stainless steel reactor vacuum, } -195\,^{\circ}C} RCOOCl \qquad (1140)$$

$$RCOOCl + \diagup C{=}C \diagdown \xrightarrow[\text{2. Warmed over 1 day to } 22\,^{\circ}C]{\text{1. Evacuated glass-bulb, } -150\,^{\circ}C} RCOOC{-}CCl \qquad (1141)$$

$$RCOOH + NaF \xrightarrow[\text{3. Warmed over 6 h to } -78\,^{\circ}C \text{ 4. After 1 day ClF removed under vacuum and olefin added}]{\text{1. Kel-F reactor, } -195\,^{\circ}C, ClF \text{ 2. Brought to } -111\,^{\circ}C} RCOOC{-}CCl \qquad (1142)$$

R	Olefin	Product	Yield (%) Method A	Method B
CF_3	$CF_2{=}CF_2$	$CF_3COOCF_2CF_2Cl$	54	47
CF_3	$CF_2{=}CH_2$	$CF_3COOCF_2CH_2Cl$	94	56
CF_3	$CF_2{=}CFCl$	$CF_3COOCFClCF_2Cl$	—	65
CF_3	$CF_2{=}CCl_2$	$CF_3COOCCl_2CF_2Cl$	—	81
CF_3	$CH_2{=}CH_2$	$CF_3COOCH_2CH_2Cl$	—	33
CF_3	$CFH{=}CFH$ (*cis*)	$CF_3COOCFHCFHCl$ (*erythro*)	—	64
CF_3	$CFH{=}CFH$ (*trans*)	$CF_3COOCFHCFHCl$ (*threo*)	—	65
C_2F_5	$CF_2{=}CF_2$	$C_2F_5COOCF_2CF_2Cl$	65	53
C_2F_5	$CF_2{=}CH_2$	$C_2F_5COOCF_2CH_2Cl$	80	50
n-C_3F_7	$CF_2{=}CF_2$	n-$C_3F_7COOCF_2CF_2Cl$	66	49
n-C_3F_7	$CF_2{=}CH_2$	n-$C_3F_7COOCF_2CH_2Cl$	64	80
$ClCF_2$	$CF_2{=}CF_2$	$ClCF_2COOCF_2CF_2Cl$	17	42
$ClCF_2$	$CF_2{=}CH_2$	$ClCF_2COOCF_2CH_2Cl$	43	93
HCF_2	$CF_2{=}CF_2$	$HCF_2COOCF_2CF_2Cl$[a]	<1	<1
HCF_2	$CF_2{=}CH_2$	$HCF_2COOCF_2CH_2Cl$	17	95

[a]Structure is in question.



(1143)

Under the influence of ruthenium catalysts, carboxylic acids may also be added across acetylene triple bonds to produce vinyl esters. This approach may be used to add unsaturated carboxylic acids to terminal acetylenes if the reaction is catalyzed by bis(η^5-cyclooctadienyl)ruthenium(II)-tributylphosphine(CORuBu$_3$P)[2173] (equation 1144), or to add saturated aliphatic or aromatic carboxylic acids to di- and monosubstituted acetylenes in the presence of ruthenium carbonyl catalysts[2174] (equation 1145). The results of both of these approaches are reported in Table 105.

$$\begin{matrix} R^2 & R^1 \\ \diagdown & \diagup \\ & C{=}CCOOH \\ \diagup & \diagdown \\ R^3 & \end{matrix} + HC{\equiv}CR^4 \xrightarrow[CoRuBuP]{\text{sealed tube, } C_6H_6, 80^\circ C, 4h,}$$

$$\underset{\text{(major)}}{R^2R^3CHCHR^1COOCR^4{=}CR_2} + \underset{\text{(minor)}}{R^2R^3C{=}CR^1COOCH{=}CHR^4} \qquad (1144)$$

$$R^1COOH + R^2C{\equiv}CR^2 \xrightarrow[MeC_6H_5, N_2, 145^\circ C]{Ru_3(CO)_{12} \text{ or } [Ru(CO)_2(OAc)]_n}$$

$$\underset{(E+Z)}{R^1COOCR^2{=}CHR^2} + R^1COOCH{=}CR_2{}^2 \qquad (1145)$$

9. By reaction of ortho esters

γ- and δ-Unsaturated carboxylic acid esters have been prepared by the reaction of allyl alcohols with ortho esters in the presence of phenol (equation 1146). Details of individual reactions are reported in Table 106, and it appears that in most of the reactions a rearrangement to the most stable allyl carbonium ion occurs before the condensation to produce the ester product.

$$R^1_2C{=}CHCH_2OH + R^2C(OR^3)_3 \xrightarrow[130\text{–}140^\circ C]{PhOH} H_2C{=}CHCR^1_2CH_2COOR^3 \qquad (1146)$$

Cyclic ortho esters of *cis*- and *trans*-cyclohexanediols and their analogs have been converted[2181] into their corresponding orthoacetate esters upon treatment with trimethylsilyl chloride. The general reaction of this conversion is illustrated in equation 1147, while a series of specific reactions are reported in Table 107.

(1147)

10. By alcoholysis of di- and trihalides

Reactions of *gem*-dihalides with alcohols in the presence of an acid or base produce carboxylic acid esters. One recent procedure[2182] which embodies this approach is the reaction of 1,1-dichloroethenes with an alcoholic reagent which readily forms a tertiary alkyl carbonium ion in concentrated sulfuric acid, followed by reaction with the substrate alcohol and hydrolysis of the unisolated intermediate dihalide (equation 1148). This procedure affords a direct method of preparation of tertiary alkylacetic esters.

TABLE 105. Ruthenium catalyst addition of carboxylic acids to acetylenes

Acid	Alkyne	Catalyst	Temp. (°C)	Time (h)	Product	Yield (%)	Reference
MeCOOH	PhC≡CPh	$Ru_3(CO)_{12}$	145	22	MeCOOCPh=CHPh(*E*) +	45	2174
					MeCOOCPh=CHPh(*Z*) +	5	
					MeCOOCH=CPh_2	5	
MeCOOH	PhC≡CPh	$[Ru(CO)_2(OAc)]_n$	145	19	MeCOOCPh=CHPh(*E*) +	42.5	2174
					MeCOOCPh=CHPh(*Z*) +	3.5	
					MeCOOCH=CPh_2	4.0	
MeCOOH	*n*-PrC≡CPr-*n*	$Ru_3(CO)_{12}$	145	17	MeCOOC(Pr-*n*)=CHPr-*n*	92	2174
MeCOOH	MeOOCC≡CCOOMe	$Ru_3(CO)_{12}$	145	17	MeCOOC(COOMe)=CHCOOMe	95	2174
t-BuCOOH	PhC≡CPh	$Ru_3(CO)_{12}$	145	20	*t*-BuCOOCPh=CHPh(*E*) +	67	2174
					t-BuCOOCPh=CHPh(*Z*) +	9	
					t-BuCOOCH=CPh_2	Trace	
CH_2=CMeCOOH	*n*-PrC≡CPr-*n*	*a*	80	4	H_2C=C(Me)COOC(*n*-Pr)=CH_2 +	66	2173
					H_2C=C(Me)COOCH=CH(Pr-*n*)(*E*) +	Trace	
					H_2C=C(Me)COOCH=CH(Pr-*n*)(*Z*)	Trace	
MeCH=CHCOOH(*E*)	*n*-PrC≡CH	*a*	80	4	MeCH=CHCOOC(Pr-*n*)=CH_2(*E*)	50	2173
MeCH=CH=COOH(*E*)	*t*-BuC≡CH	*a*	80	4	MeCH=CHCOOC(Bu-*t*)=CH_2(*E*)	68	2173

$CH_2{=}CHCH_2COOH$	*n*-PrC≡CH	*a*	80	8	$CH_2{=}CHCH_2COOC(Pr\text{-}n){=}CH_2$	40	2173
$MeCH{=}CHCH{=}$ CHCOOH (*E*,*E*)	*n*-PrC≡CH	*a*	80	4	$MeCH{=}CHCH{=}CHCOOC(Pr\text{-}n){=}CH_2$ (*E*,*E*)	79	2173
PhCOOH	*n*-PrC≡CH	*a*	80	4	$PhCOOC(Pr\text{-}n){=}CH_2$	75	2173
PhCOOH	PhC≡CPh	$Ru_3(CO)_{12}$	145	17	$PhCOOCPh{=}CHPh(E)+$ $PhCOOCPh{=}CHPh(Z)+$ $PhCOOCH{=}CPh_2$	11 53 17	2174
PhCOOH	PhC=CPh	$[Ru(CO)_2(OAc)]_n$	145	20	$PhCOOCPh{=}CHPh(E)+$ $PhCOOPh{=}CHPh(Z)+$ $PhCOOCH{=}CPh_2$	13 40 13	2174
PhCOOH	PhC≡CH	$Ru_3(CO)_{12}$	145	17	$PhCOOCH{=}CHPh(E)+$ $PhCOOCH{=}CHPh(Z)+$ $PhCOOCPh{=}CH_2$	59.5 14.5 22	2174
p-FC_6H_4COOH	Ph≡CPh	$Ru_3(CO)_{12}$	145	19	*p*-$FC_6H_4COOCPh{=}CHPh(E+Z)+$ *p*-$FC_6H_4COOCH{=}CPh_2$	19 26	2174
p-MeC_6H_4COOH	PhC≡CPh	$Ru_3(CO)_{12}$	145	19	*p*-$MeC_6H_4COOCPh{=}CHPh(E+Z)+$ *p*-$MeC_6H_4COOCH{=}CPh_2$	32 8	2174

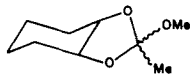
[a]Catalyst used in bis(η^5-cyclooctadienyl)ruthenium(II)-tri(*n*-butyl)phosphine.

TABLE 106. Esters by reaction of ortho esters with olefins

Olefin	Ortho ester	Temp. (°C)	Time (h)	Product	Yield (%)	Reference
$Me_2C{=}CHCH_2OH$	$MeC(OEt)_3$	135–140	9–10	$H_2C{=}CHCMe_2CH_2COOEt$	78	2175
$Me_2C{=}CHCH_2OH$	$MeC(OEt)_3$	140	15	$H_2C{=}CHCMe_2CH_2COOEt$	—	2176
$Me_2C{=}CHCH_2OH$	$MeC(OEt)_3$	140	15	$H_2C{=}CHCMe_2CH_2COOEt$ +	65	2177
				$H_2C{=}CHCMe_2CH_2COOCH_2CH{=}CMe_2$	15	
$Me_2C{=}CHCHMeOH$	$MeC(OEt)_3$	135–140	9–10	$H_2C{=}CHCHMeCH_2COOEt$	—	2175
$Me_2C{=}CHCHEtOH$	$MeC(OEt)_3$	135–140	9–10	$H_2C{=}CHCHEtCH_2COOEt$	—	2175
$Me_2C{=}CHCMe_2OH$	$MeC(OEt)_3$	135–140	9–10	$H_2C{=}CHCMe_2CH_2COOEt$	—	2175
$H_2C{=}CHCMe_2OH$	$MeC(OEt)_2(OC_8H_{17}\text{-}n)$[a]	140	7	$H_2C{=}CHCMe_2CH_2COOC_8H_{17}\text{-}n$	—	2178
$H_2C{=}CHCMe_2OH$	$MeC(OEt)_2(OCH_2Ph)$[a]	140	7	$H_2C{=}CHCMe_2CH_2COOCH_2Ph$	—	2178
$H_2C{=}CHCMe_2OH$	$MeC(OEt)_2(OCH_2C_6H_4OPh\text{-}m)$[a]	140	7	$H_2C{=}CHCMe_2CH_2COOCH_2C_6H_4OPh\text{-}m$	—	2178
$Me_2C{=}CHCH(OH)CCl_2CHClMe$	$MeC(OEt)_3$[a]	130–135	44	$EtOOCCH_2CMe_2CHClCH{=}CClCHClMe$	74	2179
$Me_2C{=}CHCH(OH)CCl_2CHClMe$	$EtC(OEt)_3$[a]	130–135	4	$EtOOCCHMeCMe_2CHClCH{=}CClCHClMe$	—	2179
$Me_2C{=}CHCH(OH)CCl_2CH_2Cl$	$MeC(OEt)_3$[a]	130–135	4	$EtOOCCH_2CMe_2CHClCH{-}CClCH_2Cl$	—	2179
$Me_2C{-}CHCH(OH)CClBrCH_2Cl$	$MeC(OEt)_3$[a]	130–135	4	$EtOOCCH_2CMe_2CHBrCH{-}CClCH_2Cl$ +		2179
				$EtOOCCH_2CMe_2CHClCH{=}CBrCH_2Cl$	—	
$H_2C{=}CHCH_2CH(OH)CH{=}CMe_2$	$MeC(OEt)_3$	140	20	$H_2C{=}CHCH_2CH{=}CHCMe_2CH_2COOEt$	87	2180
$PhCH_2CH{=}CHCMe_2OH$	$MeC(OEt)_3$	140	20	$PhCH_2CH{=}CHCMe_2CH_2COOEt$	—	2180

[a]A mixture of phenol and 2-methylpropanoic acid was used as catalyst.

TABLE 107. Preparation of ethanoates from cyclic ortho esters[2181]

Ortho ester	Ethanoate	Yield (%)
		—
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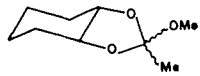
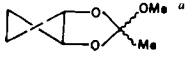
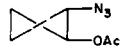
	N.R.	—
trans		
 [a]		40
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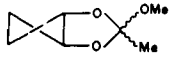		86
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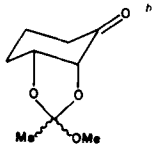
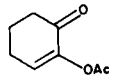
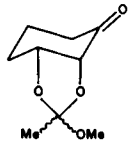
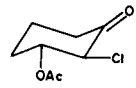
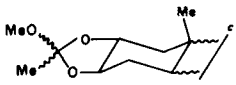
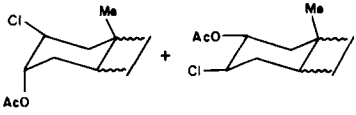
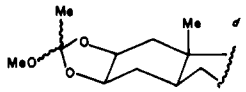
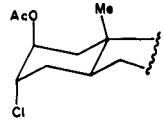
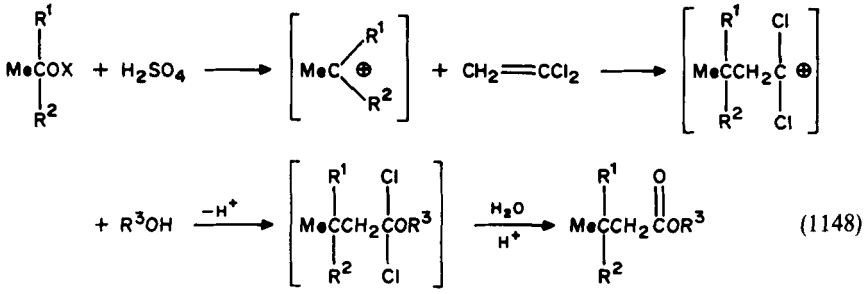
 [b]		65
cis		
		14
cis	*trans*	
 [c]		6 + 50
	trans-diequatorial	50
 [d]		73
	trans-diaxial	

[a] Reagent used Me_3SiN_3.
[b] Reagent used Me_3SiOAc.
[c] Active portion of 5α-cholestan-2α, 3α-diol.
[d] Active portion of 5α-cholestan-2β,3β-diol.



(1148)

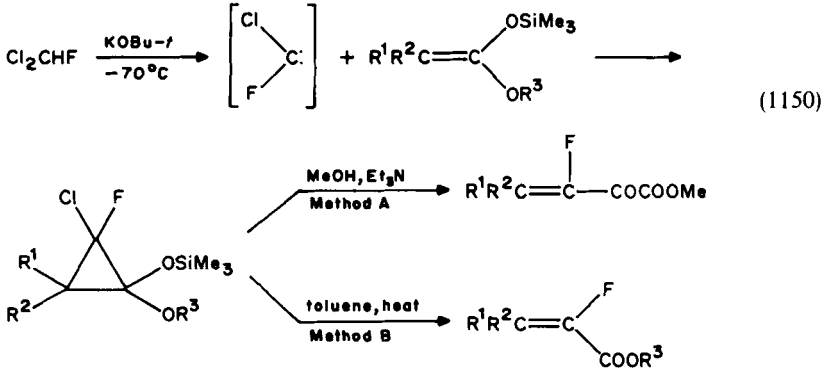
R^1	R^2	X	R^3	Temp. (°C)	Yield (%)
Me	Me	H	Me	40	63
Me	Me	H	Me	75	76
Me	Me	Me	Me	40	68
Me	Me	H	Et	40	50
Me	Me	H	*n*-Pr	40	52
Me	Me	H	*i*-Pr	40	34
Me	Me	H	*n*-Bu	40	46
Me	Me	H	*i*-Bu	40	43
Me	Me	H	*m*-Pen	40	42
Et	Me	H	Me	75	49
Et	Et	H	Me	75	13

Base-catalyzed methanolysis of 1,1-dichloroalkyl phenyl sulfides produces[2183] the corresponding methyl esters in fair to good yields (equation 1149).

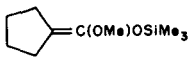
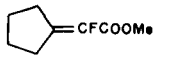
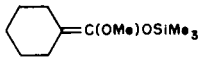
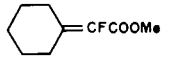
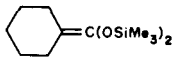
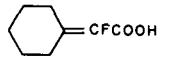
$$RCCl_2SPh + MeOH \xrightarrow[-5\,°C,\,30\,min]{H_2O,\,Na_2CO_3} RCOOMe \qquad (1149)$$

R =	*n*-Pen	n-C_7H_{15}	n-C_8H_{17}	$Ph(CH_2)_2$
Yield (%) =	70	70	76	41

Addition of chlorofluorocarbene to enoxy silanes produces chlorofluoro trialkysiloxycyclopropanes which, upon treatment with methanol and base (Method A, equation 1150),

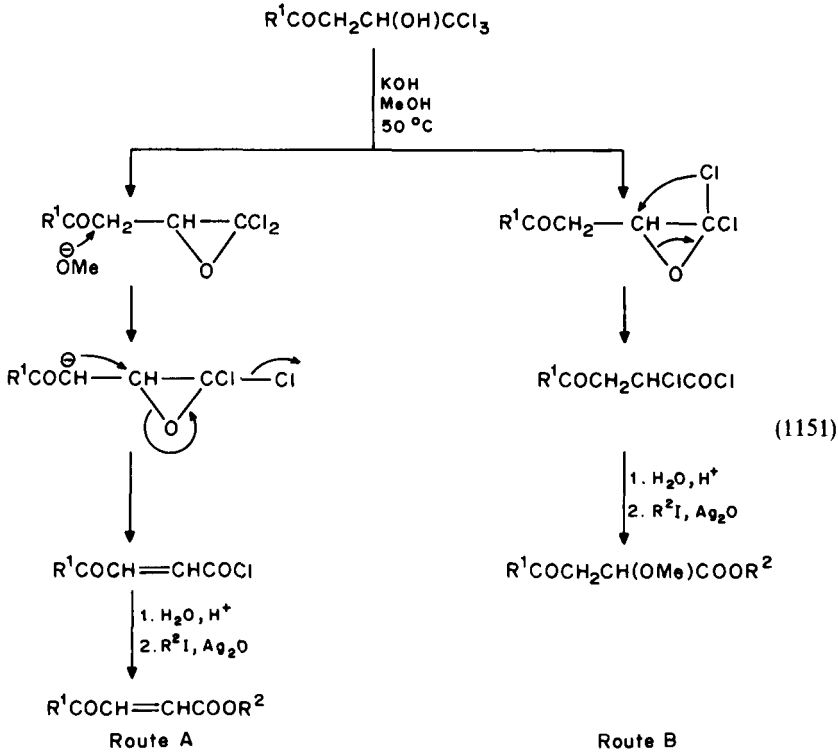


(1150)

Enoxysilane	Ratio *E*:*Z*	Method	Product	Ratio *E*:*Z*	Yield (%)
n-PenCH=C(OEt)OSiMe$_3$	82:18	A	*n*-PenCH=CFCOOMe	37:63	80
PhCH=C(OEt)OSiMe$_3$	70:30	A	PhCH=CFCOOMe	42:58	80
PhCH=C(OEt)OSiMe$_3$	70:30	B	PhCH=CFCOOEt	41:59	94
Me$_2$C=C(OHex-*n*)OSiMe	—	B	Me$_2$C=CFCOOHex-*n*	—	94
	—	A		—	85
	—	A		—	95
	—	A		—	80
n-PenCH=C(OMe)OSiMe$_2$Bu-*t*	14:86	A	*n*-PenCH=CFCOOMe	43:57	90
n-PenCH=C(OMe)OSiMe$_2$Bu-*t*	82:18	A	*n*-PenCH=CFCOOMe	40:60	90

afford α-fluoro α,β-ethylenecarbonylcarboxylic acid esters. However, thermolysis[2184] of the same cyclopropanes in toluene produces the α-fluoro α,β-ethylenecarboxylic acid esters (Method B, equation 1150).

In the trihalide series, alkaline methanolysis of 1,1,1-trichloro-2-hydroxy-4-alkanones has been reported[2185] to produce a variety of α,β-unsaturated and β-methoxy saturated



(1151)

Trihalides	R^2	Products (ratio)
$MeCOCH_2CH(OH)CCl_3$	Me	$MeCOCH(OMe)CH_2COOMe$ + $MeCOCH_2CH(OMe)COOMe$ + $MeCOCH{=}CHCOOMe$ + $ClCH{=}CHCH{=}CHCOOMe$ (10:4:3:2)
$Me_2CHCH_2COCH_2CH(OH)CCl_3$	Me	$Me_2CHCH_2COCH_2CH(OMe)COOMe$ + (17.5%) $Me_2CHCH_2COCH(OMe)CH_2COOMe$ + (20%) $Me_2CHCH_2COCH{=}CHCOOMe$ (60%) (24:8:7)
$Me_2CHCH_2COCH_2CH(OH)CCl_3$	*n*-Bu	$Me_2CHCH_2COCH_2CH(OMe)COOBu\text{-}n$ + $Me_2CHCH_2COCH(OMe)CH_2COOBu\text{-}n$ + $Me_2CHCH_2COCH{=}CHCOOBu\text{-}n$
$Me_3COCH_2CH(OH)CCl_3$	Me	$Me_3CCOCH_2CH(OMe)COOMe$ + $Me_3CCOCH{=}CHCOOMe$ (15:1)

methyl esters as reported below. The mechanism proposed for the reaction is similar to the mechanism proposed by Reeve and coworkers[2186,2187] for the alkaline methanolysis of aryl (trichloromethyl)carbinols, and proceeds via the formation of an α,α-dichloroepoxide, which undergoes ring opening either by nucleophilic attack of methoxide ion at the aryl-substituted carbon, followed by acyl chloride hydrolysis (Route A, equation 1151), or by an α-chloroepoxide-α-chloro carbonyl rearrangement followed by methanolysis of the intermediate α-chloroacyl chloride (Route B, equation 1151).

11. From aldehydes

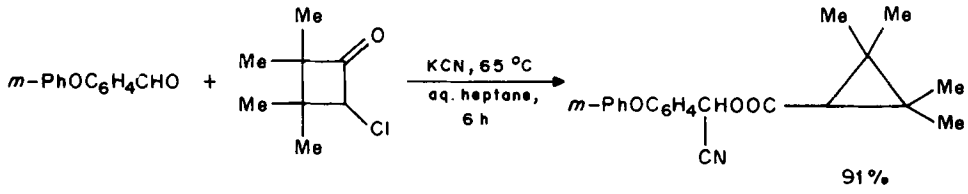
The carboxylic acid ester preparations presented in this section are those which involve an aldehyde, whether preformed or formed as an intermediate, as the starting material.

Preparation of carboxylic acid esters from preformed aldehydes may involve oxidation, as in the reaction[2188] of benzaldehyde with methanol in the presence of ruthenium trichloride and the methyl iodide-tri(*n*-butyl)phosphine complex (equation 1152) to produce methyl benzoate.

$$PhCHO + MeOH \xrightarrow[\substack{MeI\text{-}P(Bu\text{-}n)_3 \\ 160\,^{\circ}C,\,5\,h}]{RhCl_3\cdot 3H_2O,} PhCOOMe \qquad (1152)$$

Another preparation of esters from preformed aldehydes involves the condensation[2189] of *m*-phenoxybenzaldehyde and 2-chloro-3,3,4,4-tetramethylcyclobutanone in the presence of potassium cyanide (equation 1153). Under the conditions of the reaction a ring contraction occurs to produce a substituted cyclopropanecarboxylic acid ester.

Reaction[2190] of aliphatic aldehydes with *O*-methyl-*C*,*O*-bis(trimethylsilyl) ketene acetal in the presence of a Lewis acid permits a stereocontrolled synthesis of α,β-unsaturated esters (equation 1154). In order to investigate the results obtained from this reaction using a variety of Lewis acid catalysts and reaction conditions, a study[2190] of the reaction using



(1153)

$$RCHO + Me_3SiCH{=}C(OMe)OSiMe_3 \xrightarrow{\text{Lewis acid}} \underset{(E:Z = 3:1)}{} [RCHOHCH(SiMe_3)COOMe] \rightarrow \underset{(E:Z \text{ mixture})}{RCH{=}CHCOOMe} \quad (1154)$$

R = *i*-Pr, *n*-Hex, *n*-C_8H_{17}, Ph

$$n\text{-}C_8H_{17}CHO + Me_3SiCH{=}C(OMe)OSiMe_3 \xrightarrow{\text{Lewis acid}} \underset{(E:Z = 3:1)}{} n\text{-}C_8H_{17}CH{=}CHCOOMe \quad (1155)$$

Lewis acid	Solvent	Conditions	Yield (%)	*E*:*Z*
$TiCl_4$	CH_2Cl_2	−95 °C, 3 h then r.t., 2 h	91	14:86
$TiCl_4$	CH_2Cl_2	r.t., 3 h	82	27:73
$TiCl_4$	CH_2Cl_2	−78 °C, 3 h then r.t., 2 h	90	5:95[a]
$BF_3 \cdot Et_2O$	CH_2Cl_2	−95 °C, 3 h, then r.t., 2 h	90	23:77
$AlCl_3$	C_6H_6	Reflux 8 h	70	89:11
$AlCl_3$	CCl_4	Reflux 8 h	89[b]	93:7
$AlCl_3$	CCl_4	Reflux 8 h	73[b]	96:4[a]
$ZnCl_2$	C_6H_6/THF	Reflux 6 h	56	96:4
$ZnCl_2$	MeC_6H_5/THF	Reflux 22 h	92	69:31

[a]Z-rich starting ketene acetal (*E*:*Z* = 5:95) was used, otherwise *E*-rich starting ketene acetal (*E*:*Z* = 3:1) was used.
[b]Two moles of ketene acetal was used.

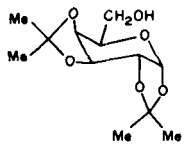
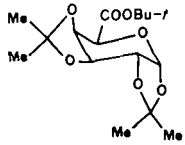
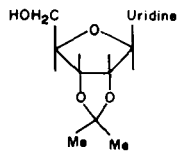
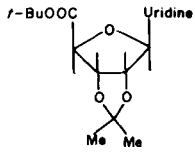
nonanal for the production of methyl undec-2-enoate was undertaken (equation 1155). The results of this study indicated that titanium tetrachloride gave mainly the *Z* isomer, while aluminum chloride gave mainly the *E* isomer. These results were obtained by the stereoselective elimination of trimethylsilyl hydroxide in an *anti* manner when titanium tetrachloride was used, while when aluminum chloride was used the results seem to be controlled by the opposite manner of elimination in each isomer of the intermediate, via the *syn* manner for the (2*R**, 3*S**) intermediate isomer and via the *anti* manner for the (2*R**, 3*R**) intermediate isomer (equation 1156).

$$n\text{-}C_8H_{17}CH(OSiMe_3)CH(SiMe_3)COOMe \xrightarrow{-Me_3SiOH} n\text{-}C_8H_{17}CH{=}CHCOOMe \quad (1156)$$

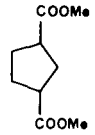
Diastereomer	Lewis acid	Conditions	Yield (%)	*E*:*Z*
(2*R**,3*S**)	$TiCl_4$	CH_2Cl_2, r.t., 1 h	93	2:98
(2*R**,3*R**)	$TiCl_4$	CH_2Cl_2, r.t., 1 h	97	99:1
(2*R**,3*S**)	$AlCl_3$	CCl_4, reflux, 6 h	78	89:11
(2*R**,3*R**)	$AlCl_3$	CCl_4, reflux, 6 h	73	80:20

Reactions involving intermediate aldehyde formation during carboxylic acid ester synthesis include the oxidative conversion[2191] of carbohydrate primary alcohols to their corresponding *t*-butyl esters (equation 1157), and the ozone oxidation[2192,2193] of olefins in alcohol using a hydrochloric acid catalyst to produce methyl esters (equation 1158).

$$RCH_2OH \xrightarrow[CH_2Cl_2,\ DMF,\ r.t.,\ 15\ min]{CrO_3\text{-}C_5H_5N(2:1)} \{RCHO\} \underset{HOCMe_3}{\overset{Ac_2O,\ 16\ h}{\rightleftharpoons}} [RCH(OH)OCMe_3] \longrightarrow RCOOCMe_3 \quad (1157)$$

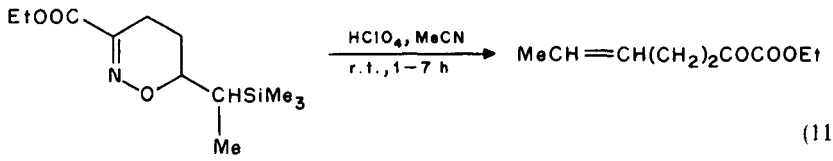
Carbohydrate 1° alcohol	Product	Yield (%)
		86
		62

$$RCH{=}CHR \xrightarrow[2.\ r.t.\ \ 3.\ O_3,\ -100\ to\ +20\ °C]{1.\ O_3,R^1OH,HCl\ \ -50°\ to\ 70\ °C} \begin{cases} RCHO \xrightarrow{R^1OH} RCH(OR^1)_2 \xrightarrow{O_3} \\ RCHOOH\ (OR^1) \xrightarrow[H_2O]{H^+} RCOOR^1 \end{cases} \quad (1158)$$

Olefin	R	Product	Yield (%)
n-$C_3H_7CH{=}CHC_3H_7$-*n* (*trans*)	Me	*n*-C_3H_7COOMe	65–67
$PhCH{=}CHPh$ (*trans*)	Me	PhCOOMe	72–86
Cyclopentene	Me	$MeOOC(CH_2)_3COOMe$	78
Cyclohexene	Me	$MeOOC(CH_2)_4COOMe$	79–85
Cyclooctene	Me	$MeOOC(CH_2)_6COOMe$	80
Cyclodecene	Me	$MeOOC(CH_2)_8COOMe$	62–82
Cyclodecene	Et	$EtOOC(CH_2)_8COOEt$	69
Cyclodecene	*n*-Pr	*n*-$PrOOC(CH_2)_8COOPr$-*n*	80
	Me	$MeOOC(CH_2)_{10}COOMe$	70
2-Norbornene	Me	 (*cis*:*trans* = 9:1)	83
1,5-Cyclooctadiene	Me	$MeOOC(CH_2)_2COOMe$	64

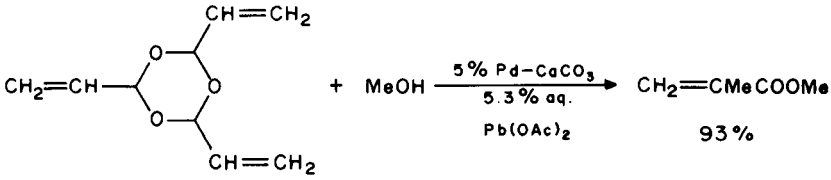
12. Hydrolytic and oxidative ring opening

Treatment[2194] of 6-trimethylsilylmethyl-5,6-dihydro-4*H*-1,2-oxazines with perchloric acid in acetonitrile produces δ,ε-unsaturated α-keto esters (equation 1159) via a hydrolytic ring opening.



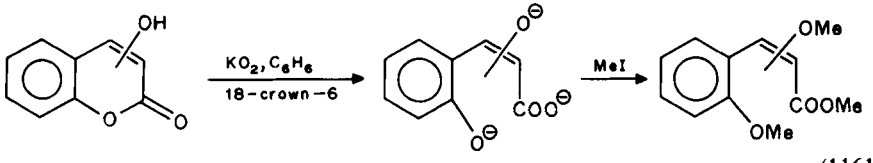
(1159)

Oxidative ring opening of methacrolein, in the presence of methanol, using palladium on calcium carbonate and aqueous lead diacetate affords[2195] methyl methacrylate (equation 1160). Even though methacrolein is a trimer of its precursor aldehyde, we consider it a better representative of oxidative ring opening than of a reaction of an aldehyde to produce an ester.

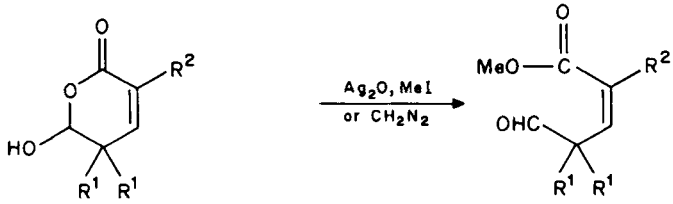


(1160)

Oxidative ring opening has also been reported[2196] to occur when 3- and 4-hydroxycoumarin (equation 1161) are treated with superoxide anion radical generated from reaction of potassium superoxide with 18-crown-6 in benzene. Trapping the intermediate trianion with methyl iodide affords the corresponding dimethoxy substituted esters. These same authors also report[2196] that treatment of substituted lactols with silver oxide in the presence of methyl iodide or diazomethane causes oxidative ring opening of the lactols and formation of the corresponding aldehydic esters (equation 1162).



(1161)



(1162)

R^1 = Me, Me, Me, Me; $R^1 - R^1$ = $-(CH_2)_5-$

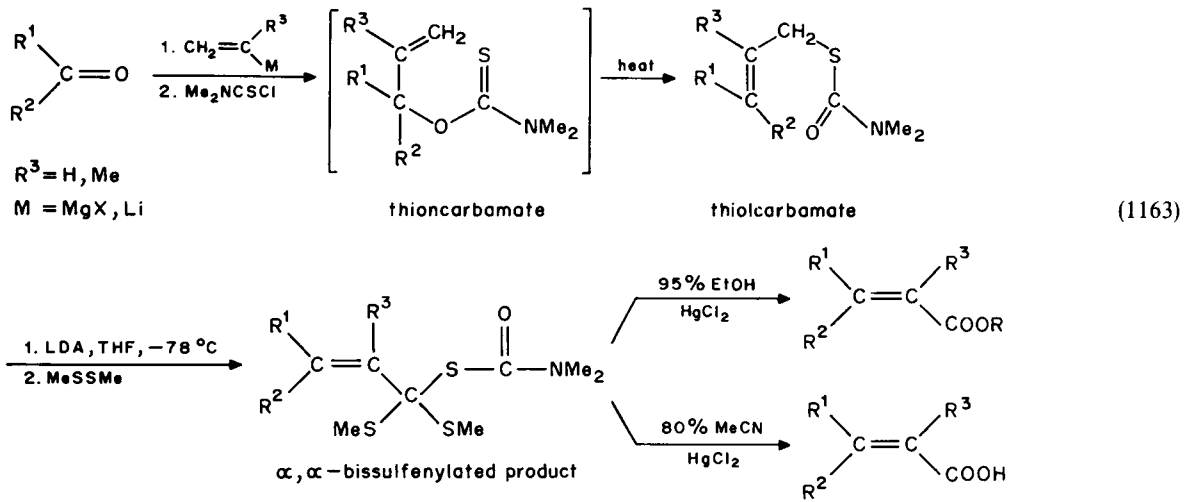
R^2 = H, OEt, OMe, Me; OMe

13. Rearrangements

Reaction[2197] of aldehydes or ketones with vinyl magnesium halide or lithium reagents produces allylic alcohols, which when allowed to react with *N,N*-dimethylthiocarbamoyl chloride produce allylic thioncarbamates. If the latter are then heated unisolated, a [3,3]-sigmatropic rearrangement occurs to produce thiolcarbamates, which upon further treatment with two equivalents of LDA in tetrahydrofuran at $-78\,^{\circ}C$ followed by addition of dimethyl disulfide produce a quantitative yield of the corresponding α,α-bissulfenylated product. This product, without purification, with $EtOH/HgCl_2$ affords good yields of the carboxylic acid esters, while using $MeCN/HgCl_2$ it produces the corresponding carboxylic acid (equation 1163).

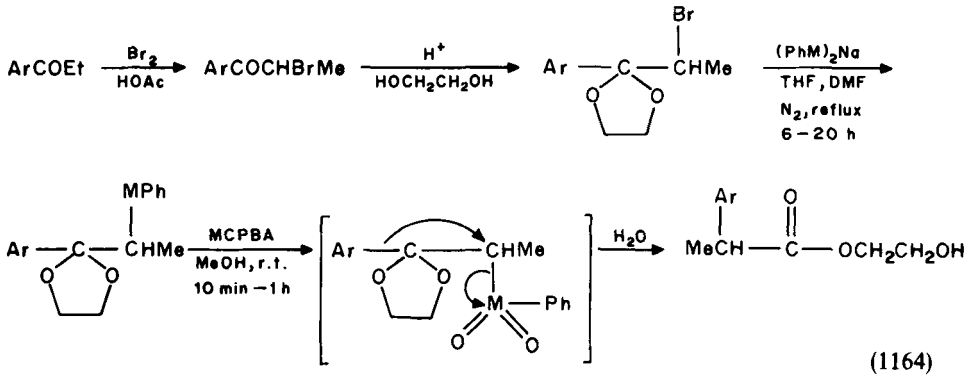
Sequential treatment[2198] of aryl ethyl ketones with bromine in acetic acid, followed by ethylene glycol in the presence of *p*-toluenesulfonic acid, and then by a tetrahydrofuran–dimethylformamide solution of diphenyl diselenide or ditelluride and sodium wire under a nitrogen atmosphere, produces the ethylene acetals of aryl α-phenylseleno- or telluro-ethyl ketones. Oxidation of these products with *m*-chloroperbenzoic acid affords hydroxyethyl 2-arylpropanoates in moderate to good yields via an aryl group rearrangement (equation 1164).

Another oxidative rearrangement reported in the recent literature[2199] concerns the synthesis of 2-arylalkanoic acid esters from α-methoxystyrene derivatives catalyzed by thallium(III) salts. This approach depends upon the observation[2199] that enol ether derivatives of alkyl aryl ketones are oxidized very selectively to 2-aryl alkanoates by a



(1163)

Thiolcarbamate	Ester or acid	Yield (%)	Stereochemistry
(*E*) *n*-PenCH=CHCH$_2$SCONMe$_2$	*n*-PenCH=CHCOOEt	17	*E* only
(*E*) *n*-HexCH=CMeCH$_2$SCONMe$_2$	*n*-HexCH=CMe—COOH	57	*E* only
Me$_2$C=CH(CH$_2$)$_2$CMe=CHCH$_2$SCONMe$_2$	Me$_2$C=CH(CH$_2$)$_2$CMe=CHCOOEt	73	*E*/*Z* = ~3.0
n-C$_3$H$_7$CMe=CHCH$_2$SCONMe$_2$	*n*-C$_3$H$_7$CMe=CHCOOEt	57	*E*/*Z* = ~3.5
(*E*)-EtCHMeCH=CMeCH$_2$SCONMe$_2$	EtCHMeCH=CMeCOOH	75	*E* only



(1164)

Ar	M	Yield (%)
Ph	Se	80
p-Tol	Se	86
p-(*i*-Bu)C_6H_4	Se	82
p-PhC_6H_4	Se	56
p-BrC_6H_4	Se	85
Ph	Te	80
p-Tol	Te	62
p-(*i*-Bu)C_6H_4	Te	85

number of simple hydrated thallium(III) salts, as well as by anhydrous salts, in the presence of trimethylorthoformate or a solid support (equation 1165). Since alkyl aryl ketones were found to be highly ketalized by trimethylorthoformate in the presence of thallium(III) salts under anhydrous conditions, a direct conversion of the parent ketone to 2-aryl alkanoates was readily accomplished by allowing the ketone to react with a hydrated thallium(III) salt with sufficient trimethyl orthoformate to insure dehydration of the intermediate salt and ketalization of the ketone (equation 1166). The results obtained using various thallium salts and reaction conditions are reported below.

$$p\text{-}(i\text{-Bu})C_6H_4C(OMe)=CHMe \xrightarrow{Tl(III)} p\text{-}(i\text{-Bu})C_6H_4CH(OMe)COOMe \quad (1165)$$

$$p\text{-}(i\text{-Bu})C_6H_4COEt + HC(OMe)_3 \xrightarrow[55\,^\circ C,\ 1.5\,h]{Tl(III)\ salt,\ MeOH} [p\text{-}(i\text{-Bu})C_6H_4C(OMe)=CHMe \longrightarrow$$

$$p\text{-}(i\text{-Bu})C_6H_4COEt + p\text{-}(i\text{-Bu})C_6H_4CHMeCOOMe + p\text{-}(i\text{-Bu})C_6H_4COCH(OMe)Me \quad (1166)$$
$$\textbf{(A)} \qquad \textbf{(B)} \qquad \textbf{(C)}$$

Thallium salt	Reaction conditions	Ratio A/B/C
$Tl(NO_3)_3\cdot 3H_2O$	MeOH, 70% aq. $HClO_4$, 0 °C, 5 min	24:72: ~ 1
$Tl(NO_3)_3\cdot 3H_2O$	MeOH, r.t., 5 min	7:92: < 1
$Tl_2(SO_4)_3\cdot nH_2O$	MeOH, 0 °C, 5 min	42:56: < 1

Thallium salt	Reaction conditions	Ratio A/B/C
$Tl_2(SO_4)_3 \cdot nH_2O$ (excess)	MeOH, 0 °C, 5 min	11:89: < 1
$Tl(ClO_4)_3 \cdot nH_2O$	MeOH, 0 °C, 5 min	16:78: < 1
$Tl(OAc)_3 \cdot 1\frac{1}{2} H_2O$	80% aq. HOAc, 25 °C, 30 min	25:72: < 1
$Tl(OAc)_3 \cdot 1\frac{1}{2} H_2O$ (excess)	80% aq. HOAc, 25 °C, 30 min	8:89: < 1
$Tl_2(SO_4)_3 \cdot nH_2O$	MeOH, NaOMe (pH = 3–5), 0–25 °C	0:100:0

14. From acylhydrazines

Reaction of acylhydrazines[2200,2201] or *N*-acyl-*N*-tosylhydrazines[2201] with copper salts effects a facile conversion to carboxylic acid esters (equation 1167). The copper salts used in these conversions were of three kinds, commercially available copper(II) chloride dihydrate, alkoxycopper(II) chloride or dialkoxycopper(II), both of the latter two salts being prepared *in situ*. The ester moiety R^3 was furnished by using an alcohol as the solvent when copper(II) chloride dihydrate was the reagent or from the *in situ* prepared reagent as in the case of the alkoxycopper(II) chloride and the dialkoxycopper(II). Table 108 lists the details of these reactions along with the products and yields obtained.

$$R^1CONHNHR^2 + Cu^{2+} \xrightarrow{\text{conditions}} R^1COOR^3 \qquad (1167)$$

The mechanism of these conversions is very much in question, since one group of authors[2200] favors an oxidative cleavage explanation, while the other group of authors[2201] favors a hydrolytic or alcoholysis process.

15. Other

High yields of thioesters have been obtained[2202] by direct reaction of carboxylic acids with tris(ethylthio)borane, and although the mechanism for this reaction is complex it appears to proceed via the intermediate formation of carboxylic anhydrides and oxybis(diacyloxy)boranes (equation 1168).

$$RCOOH + B(SEt)_3 \longrightarrow EtSH + (RCO)_2O + [(RCO)_2B]_2O \longrightarrow RCOSEt \qquad (1168)$$

Acid	Solvent	Temp. (°C)	Time (h)	Product	Yield (%)
MeCOOH	C_6H_6	80	2	MeCOSEt	77
$Me(CH_2)_4COOH$	C_6H_6	80	2	$Me(CH_2)_4COSEt$	81
$Me(CH_2)_4COOH$	Et_2O	36	6	$Me(CH_2)_4COSEt$	79
$Me_2CHCOOH$	Et_2O	36	8	$Me_2CHCOSEt$	74
Me_3CCOOH	Et_2O	36	168	$Me_3CCOSEt$	75
Me_3CCOOH	C_6H_6	80	5	$Me_3CCOSEt$	53
PhCOOH	C_6H_6	80	6	PhCOSEt	72
PhCOOH	$(MeOCH_2)_2$	85	7	PhCOSEt	78
p-AnCOOH	$(MeOCH_2)_2$	85	6	*p*-AnCOSEt	78

An interesting preparation of α-benzoylbenzyl carboxylates has been reported[2203] which occurs when olefins are hydroformylated in the presence of benzil and a rhodium catalyst (equation 1169). The olefins which have been reported[2203] to undergo this

TABLE 108. Copper salt catalyzed ester formation from acylhydrazines

Acylhydrazine	Copper salt	Reaction conditions	Product	Yield (%)	Reference
n-$C_7H_{15}CONHNH_2$	Cu(OMe)Cl	THF, 5 h, r.t.	n-$C_7H_{15}COOMe$	86	2200
n-$C_7H_{15}CONHNH_2$	Cu(OMe)Cl	DMF, 5 h, r.t.	n-$C_7H_{15}COOMe$	54	2200
n-$C_7H_{15}CONHNH_2$	Cu(OMe)Cl	C_5H_5N, 5 h, r.t.	n-$C_7H_{15}COOMe$	46	2200
n-$C_7H_{15}CONHNH_2$	Cu(OBu-n)Cl	THF, 5 h, r.t.	n-$C_7H_{15}COOBu$-n	80	2200
n-$C_7H_{15}CONHNH_2$	Cu(OC$_6$H$_{11}$-c)Cl	THF, 5 h, r.t.	n-$C_7H_{15}COOC_6H_{11}$-c	77	2200
n-$C_7H_{15}CONHNH_2$	Cu(OBu-t)Cl	THF, 5 h, r.t.	n-$C_7H_{15}COOBu$-t	77	2200
n-$C_{15}H_{31}CONHNH_2$	$CuCl_2 \cdot 2H_2O$	EtOH, r.t., stir 20–22 h	n-$C_{15}H_{31}COOEt$	80	2201
n-$C_{15}H_{31}CONHNHTs$	$CuCl_2 \cdot 2H_2O$	EtOH, r.t., stir 20–22 h	n-$C_{15}H_{31}COOEt$	95	2201
$PhCH_2CONHNH_2$	$CuCl_2 \cdot 2H_2O$	EtOH, r.t., stir 20–22 h	$PhCH_2COOEt$	95	2201
$PhCH_2CH_2COONHNHTs$	$CuCl_2 \cdot 2H_2O$	EtOH, r.t., stir 20–22 h	$PhCH_2CH_2COOEt$	95	2201
$PhCONHNH_2$	$CuCl_2 \cdot 2H_2O$	EtOH, r.t., stir 20–22 h	PhCOOEt	95	2201
PhCONHNHTs	$CuCl_2 \cdot 2H_2O$	EtOH, r.t., stir 20–22 h	PhCOOEt	95	2201
$PhCONHNH_2$	Cu(OBu-t)Cl	THF, 5 h, r.t.	PhCOOBu-t	Low	2200
$PhCONHNH_2$	Cu(OBu-t)$_2$	THF, 5 h, r.t.	PhCOOBu-t	83	2200

$$RCH{=}CH_2 + CO + H_2 + PhCOCOPh \xrightarrow[\text{or } Rh_2O_3,\ 120\,^\circ C,\ 25\text{–}60\ atm]{RhH(PPh_3)_2CO} PhCOCHPhOOCCH_2CH_2R + PhCOCHPhOOCCHMeR \quad (1169)$$

reaction include 1-propene, the isomeric butenes, 1-hexene, 1-octene, cyclohexene and cyclododecene.

Fermentation has also been used[2204] for the preparation of alkyl esters of carboxylic acids, as illustrated by the reaction of isoleucine, dextrose, magnesium sulfate and Tween 80, which were placed in a fermentor with *Geotrichum fragrans* and the mixture agitated at 25 °C. Addition of ethanol to the reaction mixture over a 25-hour period, followed by absorbent charcoal, resulted in the formation of ethyl tiglate and ethyl 2-methylbutyrate.

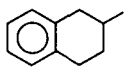
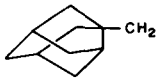
*IV. SYNTHESIS OF ACID ANHYDRIDES

Dehydrative coupling of carboxylic acids still remains the preferred method for the preparation of acid anhydrides and a large variety of new coupling agents have been reported to facilitate these preparations. In most cases an initial reaction occurs between one equivalent of the carboxylic acid and the condensing agent producing an intermediate, usually a mixed anhydride, which then reacts with a second mole of acid to produce a symmetrical acid anhydride. Where possible, in a few cases, the intermediate is isolated and allowed to react with a second equivalent of a different carboxylic acid producing mixed anhydrides.

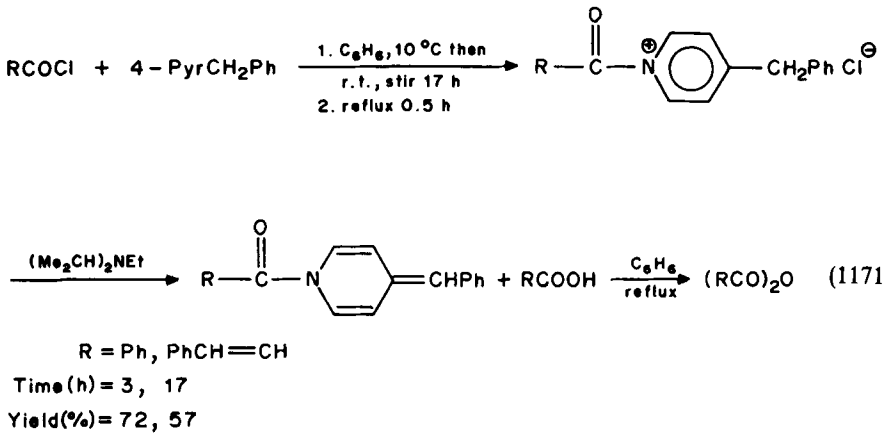
Because of the variety of condensing agents which have been used, the dehydrative coupling reactions presented in this section have been organized according to the structure of the condensing agent used, whether nitrogen, phosphorus, silicon or sulfur containing.

In the series of nitrogen-containing coupling agents which have been used recently to effect acid anhydride preparation, the simplest reagent was tetracyanoethylene[2205]. By condensation of carboxylic acids with tetracyanoethylene in benzene solution containing pyridine or some other base, symmetrical acid anhydrides can be produced (equation 1170) in yields ranging from 50 to 80 percent.

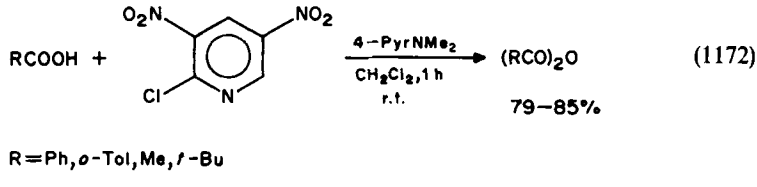
$$RCOOH + (NC)_2C{=}C(CN)_2 \xrightarrow[\text{or other base}\ 20\text{–}80\,^\circ C]{C_6H_6,\ C_5H_5N} (RCO)_2O \quad (1170)$$

R	Yield (%)	R	Yield (%)
Ph	65	*c*-HexCHPh	75
2,4,6-$Me_3C_6H_2$	67	*c*-$C_{12}H_{23}$	49
α-Naph	61	1-Ad	80
β-Naph	67		
	50		80
p-Methane-3	66		

Reaction of carboxylic acid chlorides with 4-benzylpyridine in benzene followed by treatment with ethyl di(*i*-propyl)amine produces[2206] 1-aryl-4-benzylidene-1,4-dihydropyridine. Further reaction of this intermediate with a carboxylic acid produces[2206] symmetrical acid anhydrides (equation 1171).



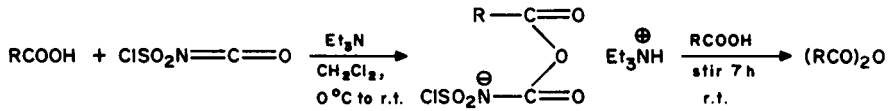
2-Chloro-3,5-dinitropyridine in the presence of 4-dimethylaminopyridine has also been reported[2207] to be an effective condensing agent for the preparation of symmetrical acid anhydrides as illustrated in equation 1172.



At least two reports[2208,2209] in the recent literature describe the production of acid anhydrides via intermediate mixed anhydride formation activated by nitrogen-containing compounds. In one report[2208] phenylacetic acid reacts with *N*-acyl-*n*-alkyl carbamoyl chloride to produce the intermediate mixed carboxylic–carbamic acid anhydride, which upon reaction with a second mole of phenylacetic acid affords the symmetrical acid anhydride (equation 1173). In the other report[2209] carboxylic acids react with chlorosulfonyl isoocyanate in the presence of triethylamine to produce the intermediate mixed carboxylic–chlorosulfonyl amine anhydride, which upon reaction with a second mole of the original acid also affords symmetrical acid anhydrides (equation 1174).

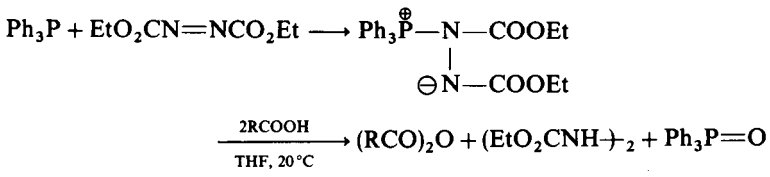
$$\mathrm{PhCH_2COOH + ClCONR^1COR^2 \longrightarrow PhCH_2COOCONR^1COR^2}$$
$$\mathrm{+\ PhCH_2COOH \longrightarrow (PhCH_2CO)_2O}$$
$$\mathrm{R^1 = Ph,\ R^2 = Me,\ R^1R^2 = (CH_2)_3} \qquad (1173)$$

In the series of phosphorous-containing coupling agents which have been used to effect acid anhydride preparation, one of the more interesting examples[2210] is the betaine formed when triphenylphosphine reacts with diethyl azodicarboxylate (DEAD). With carboxylic acids, this betaine catalyzes self-condensation of two moles of the acid, producing[2210] the corresponding symmetrical acid anhydride (equation 1175). In an attempt to determine the best phosphorous-containing coupling agent for anhydride



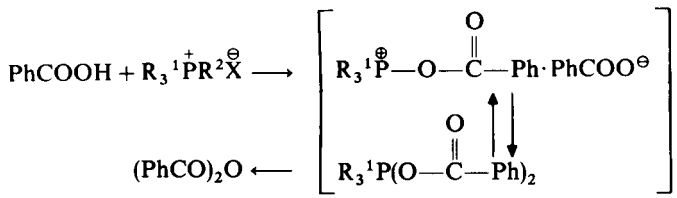
(1174)

R	Yield (%)	R	Yield (%)
Ph	79	PhCH=CH	92
p-Tol	88	MeCH=CH	86
p-An	72	*o*-$HOOCC_6H_4$	95
p-$O_2NC_6H_4$	79	(*Z*)-HOOCCH=CH	76
o-ClC_6H_4	81	$HOOC(CH_2)_2$	85
$PhCH_2$—	75		



(1175)

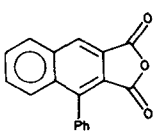
R	Yield (%)	R	Yield (%)
$HC{\equiv}C(CH_2)_2$	81	*p*-BrC_6H_4	64
i-Pr	96	$PhOCH_2$	60
n-Bu	94	PhCH=CH	75
Ph	92		

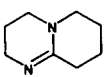


(1176)

Betaine	%Yield (benzoic acid anhydride)
$Ph_3\overset{\oplus}{P}$—N(COOH)$\overset{\ominus}{N}$COOH	92
$(EtO)_3\overset{\oplus}{P}$—N(COOH)$\overset{\ominus}{N}$COOH	Trace
$(Me_2N)_3\overset{\oplus}{P}$—N(COOH)$\overset{\ominus}{N}$COOH	Trace
$Ph_3\overset{+}{P}CCl_3\ Cl^-$	29
$(Me_2N)_3\overset{+}{P}CCl_3\ Cl^-$	69
$Ph_3\overset{+}{P}I\ I^-$	86
$(EtO)_3\overset{+}{P}I\ I^-$	Trace

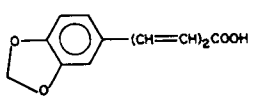
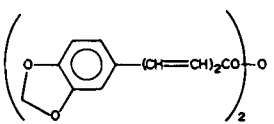
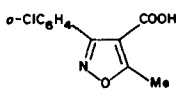
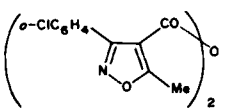
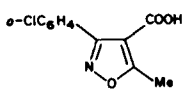
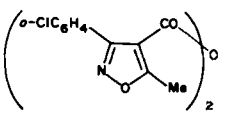
TABLE 109. Symmetrical acid anhydrides prepared using phosphorous containing coupling agents

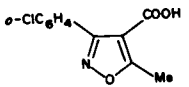
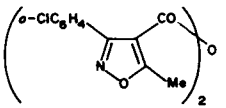
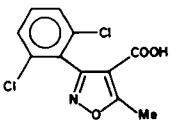
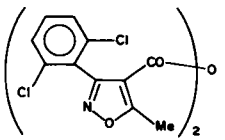
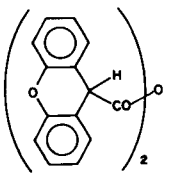
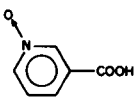
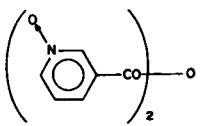
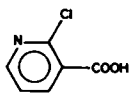
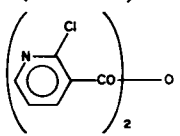
Substrate	Coupling agent	Solvent	Base	Temp. (°C)	Time (h)	Product	Yield (%)	References
HCOOH	*a*	None	N-EtPip	20	—	Decomposition	—	2211
MeCOOH	*b*	CH_2Cl_2	Et_3N	−10 to 0	—	$(MeCO)_2O$	—	2212
EtCOOH	*b*	CH_2Cl_2	Et_3N	−10 to 0		$(EtCO)_2O$		2212
n-PrCOOH	*a*	CH_2Cl_2	Et_3N	20	0.5	$(n\text{-PrCO})_2O$	95	2211
n-PenCOOH	*c*	CH_2Cl_2	Et_3N	r.t.	0.75	$(n\text{-PenCO})_2O$	92	2213
n-HexCOOH	*a*	CH_2Cl_2	Et_3N	20	0.5	$(n\text{-HexCO})_2O$	97	2211
n-BuCHEtCOOH	*a*	CH_2Cl_2	Et_3N	20	0.5	$(n\text{-BuCHEtCO})_2O$	96	2211
$n\text{-C}_8H_{17}COOH$	*a*	CH_2Cl_2	Et_3N	20	0.75	$(n\text{-C}_8H_{17}CO)_2O$	96	2211
$n\text{-C}_{11}H_{23}COOH$	*a*	CH_2Cl_2	Et_3N	20	0.5	$(n\text{-C}_{11}H_{23}CO)_2O$	98	2211
$n\text{-C}_{11}H_{23}COOH$	*c*	CH_2Cl_2	Et_3N	r.t.	0.5	$(n\text{-C}_{11}H_{23}CO)_2O$	90	2213
$n\text{-C}_{11}H_{23}COOH$	*d*	CH_2Cl_2	Et_3N	r.t.	0.5	$(n\text{-C}_{11}H_{23}CO)_2O$	91	2213
$n\text{-C}_{15}H_{31}COOH$	*a*	CH_2Cl_2	Et_3N	20	0.75	$(n\text{-C}_{15}H_{31}CO)_2O$	94	2211
$n\text{-C}_{17}H_{35}COOH$	*a*	CH_2Cl_2	Et_3N	20	0.5	$(n\text{-C}_{17}H_{35}CO)_2O$	97	2211
$BrCH_2COOH$	*a*	CH_2Cl_2	Et_3N	20	0.75	$(BrCH_2CO)_2O$	92	2211
$PhCH_2COOH$	*a*	CH_2Cl_2	Et_3N	20	0.5	$(PhCH_2CO)_2O$	99	2211
$PhOCH_2COOH$	*a*	CH_2Cl_2	Et_3N	20	0.5	$(PhOCH_2CO)_2O$	95	2211
t-BuCOOH	*a*	CH_2Cl_2	Et_3N	20	3	$(t\text{-BuCO})_2O$	90	2211
t-BuCOOH	*c*	CH_2Cl_2	Et_3N	r.t.	1	$(t\text{-BuCO})_2O$	90	2213
$H_2C{=}CMeCOOH$	*a*	CH_2Cl_2	Et_3N	20	0.5	$(H_2C{=}CMeCO)_2O$	99	2211
$MeCH{=}CHCOOH$	*a*	CH_2Cl_2	Et_3N	20	0.5	$(MeCH{=}CHCO)_2O$	100	2211
$Me_2C{=}CHCOOH$	*a*	CH_2Cl_2	Et_3N	20	0.5	$(Me_2C{=}CHCO)_2O$	98	2211
$PhCH{=}CHCOOH$	*a*	CH_2Cl_2	Et_3N	20	0.5	$(PhCH{=}CHCO)_2O$	97	2211
$PhCH{=}CHCOOH$	*c*	Me_2CO	Et_3N	r.t.	0.5	$(PhCH{=}CHCO)_2O$	91	2213
$PhCH{=}CHCOOH$	*d*	CH_2Cl_2	Et_3N	r.t.	0.5	$(PhCH{=}CHCO)_2O$	92	2213
$PhCH{=}CHCOOH$	Cl_3PO	CH_2Cl_2	C_5H_5N	r.t.	0.25	$(PhCH{=}CHCO)_2O$	90	2214
$PhC{\equiv}CCOOH$	*a*	CH_2Cl_2	Et_3N	20	0.75		~100	2211

PhCOOH	*a*	CH_2Cl_2	Et_3N	r.t.	0.5	$(PhCO)_2O$	99	2211
PhCOOH	*b*	Et_2O	Et_3N	− 10 to 0	—	$(PhCO)_2O$	—	2212
PhCOOH	*c*	CH_2Cl_2	Et_3N	r.t.	0.5	$(PhCO)_2O$	98	2213
PhCOOH	*d*	CH_2Cl_2	Et_3N	r.t.	0.5	$(PhCO)_2O$	97	2213
PhCOOH	PPSE[e]	—	$PhNH_2$	25	—	$(PhCO)_2O$	—	2215
PhCOOH	$PhOPCl_2$	DMF	C_5H_5N	—	—	$(PhCO)_2O$	—	2216
o-TolCOOH	*a*	CH_2Cl_2	Et_3N	20	0.5	$(o\text{-TolCO})_2O$	99	2211
o-TolCOOH	$PhOPCl_2$	DMF	C_5H_5N	—	—	$(o\text{-TolCO})_2O$	—	2216
m-TolCOOH	$PhOPCl_2$	DMF	C_5H_5N	—	—	$(n\text{-TolCO})_2O$	—	2216
p-TolCOOH	*b*	CH_2Cl_2	Et_3N	− 10 to 0	—	$(p\text{-TolCO})_2O$		2212
p-TolCOOH	$PhOPCl_2$	DMF	C_5H_5N	—	—	$(p\text{-TolCO})_2O$	—	2216
m-AnCOOH	$PhOPCl_2$	DMF	C_5H_5N	—	—	$(m\text{-AnCO})_2O$	—	2216
p-AnCOOH	$PhOPCl_2$	DMF	C_5H_5N	—	—	$(p\text{-AnCO})_2O$		2216
o-ClC_6H_4COOH	*a*	THF	*N*-EtPyr	20	0.5	$(o\text{-}ClC_6H_4CO)_2O$	94	2211
o-ClC_6H_4COOH	*c*	CH_2Cl_2	*N*-EtPyr	r.t.	0.5	$(o\text{-}ClC_6H_4CO)_2O$	97	2213
o-ClC_6H_4COOH	$PhOPCl_2$	DMF	C_5H_5N	—	—	$(o\text{-}ClC_6H_4CO)_2O$	—	2216
p-ClC_6H_4COOH	*a*	MeCN	$(n\text{-Bu})_3N$	20	0.5	$(p\text{-}ClC_6H_4CO)_2O$	97	2211
p-ClC_6H_4COOH	*a*	CH_2Cl_2	Et_3N	20	0.08	$(p\text{-}ClC_6H_4CO)_2O$	80	2211
p-ClC_6H_4COOH	*a*	MeCN	Et_3N	20	0.08	$(p\text{-}ClC_6H_4CO)_2O$	80	2211
p-ClC_6H_4COOH	*a*	CH_2Cl_2	C_5H_5N	20	16.6	$(p\text{-}ClC_6H_4CO)_2O$	55	2211
p-ClC_6H_4COOH	*a*	MeCN	C_5H_5N	20	3	$(p\text{-}ClC_6H_4CO)_2O$	70	2211
p-ClC_6H_4COOH	*a*	CH_2Cl_2	4-$PyrNMe_2$	20	0.08	$(p\text{-}ClC_6H_4CO)_2O$	90	2211
p-ClC_6H_4COOH	*a*	MeCN	4-$PyrNMe_2$	20	0.08	$(p\text{-}ClC_6H_4CO)_2O$	90	2211
p-ClC_6H_4COOH	*a*	CH_2Cl_2	2,6-Dimethylpyridine	20	1	$(p\text{-}ClC_6H_4CO)_2O$	0	2211
p-ClC_6H_4COOH	*a*	MeCN	2,6-Dimethylpyridine	20	1	$(p\text{-}ClC_6H_4CO)_2O$	61	2211
p-ClC_6H_4COOH	*a*	MeCN		20	0.08	$(p\text{-}ClC_6H_4CO)_2O$	90	2211
p-ClC_6H_4COOH	*c*	CH_2Cl_2	Et_3N	r.t.	0.5	$(p\text{-}ClC_6H_4CO)_2O$	91	2213
p-ClC_6H_4COOH	*d*	CH_2Cl_2	Et_3N	r.t.	0.5	$(p\text{-}ClC_6H_4CO)_2O$	92	2213
p-ClC_6H_4COOH	$PhOPOCl_2$	CH_2Cl_2	C_5H_5N	r.t.	0.25	$(p\text{-}ClC_6H_4CO)_2O$	90	2214
p-ClC_6H_4COOH	$PhOPCl_2$	DMF	C_5H_5N	—	—	$(p\text{-}ClC_6H_4CO)_2O$	—	2216

(*continued*)

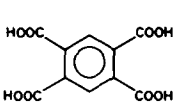
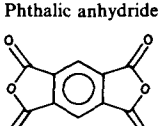
TABLE 109 (*continued*)

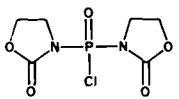
Substrate	Coupling agent	Solvent	Base	Temp. (°C)	Time (h)	Product	Yield (%)	References
m-$O_2NC_6H_4COOH$	*a*	MeCN	Et_3N	20	0.5	(*m*-$O_2NC_6H_4CO)_2O$	98	2211
p-$O_2NC_6H_4COOH$	*a*	CH_2Cl_2	Et_3N	20	0.5	(*p*-$O_2NC_6H_4CO)_2O$	97	2211
p-$O_2NC_6H_4COOH$	*c*	CH_2Cl_2	Et_3N	r.t.	0.5	(*p*-$O_2NC_6H_4CO)_2O$	91	2213
p-$O_2NC_6H_4COOH$	$PhOPOCl_2$	CH_2Cl_2	C_5H_5N	r.t.	0.25	(*p*-$O_2NC_6H_4CO)_2O$	55	2214
p-$O_2NC_6H_4COOH$	$PhOPOCl_2$	CH_2Cl_2	N-EtPip	r.t.	0.16	(*p*-$O_2NC_6H_4CO)_2O$	70	2214
3,5-Dimethoxybenzoic acid	*a*	Dioxane	N-EtPip	20	0.5	$(3,5\text{-}(MeO)_2C_6H_3CO)_2O$	97	2211
2,6-Dimethoxybenzoic acid	*a*	CH_2Cl_2	N-Et Pip	20	0.75	$[2,6\text{-}(MeO)_2C_6H_3CO]_2O$	97	2211
2,6-Dichlorobenzoic acid	*a*	MeCN	N-Et Pip	20	4	$(2,6\text{-}Cl_2C_6H_3CO)_2O$	91	2211
3,5-Dinitrobenzoic acid	*a*	CH_2Cl_2	N-Et Pip	20	0.5	$[3,5\text{-}(NO_2)_2C_6H_3CO]_2O$	90	2211
3,5-Dinitrobenzoic acid	*c*	CH_2Cl_2	Et_3N	r.t.	1	$[3,5\text{-}(NO_2)_2C_6H_3CO]_2O$	54	2213
3,5-Dinitrobenzoic acid	*c*	CH_2Cl_2	N-Et Pip	r.t.	0.25	$[3,5\text{-}(NO_2)_2C_6H_3CO]_2O$	48	2214
3,5-Dinitrobenzoic acid	*d*	CH_2Cl_2	Et_3N	r.t.	1	$[3,5\text{-}(NO_2)_2C_6H_3CO]_2O$	60	2213
3,5-Dinitrobenzoic acid	$PhOPOCl_2$	CH_2Cl_2	C_5H_5N	r.t.	0.16	$[3,5\text{-}(NO_2)_2C_6H_3CO]_2O$	46	2214
2,4,6-Trimethylbenzoic acid	*a*	MeCN	Et_3N	20	0.5	$(2,4,6\text{-}Me_3C_6H_2CO)_2O$	94	2211
3,4,5-Trimethoxybenzoic acid	*a*	MeCN	N-Et Pip	30	0.5	$[3,4,5\text{-}(MeO)_3C_6H_2CO]_2O$	95	2211
3,4,5-Trimethoxybenzoic acid	*c*	CH_2Cl_2	Et_3N	r.t.	1	$[3,4,5\text{-}(MeO)_3C_6H_2CO]_2O$	96	2213
3,5-Dinitro-2-methylbenzoic acid	*a*	MeCN	Et_3N	20	0.5	$[3,5\text{-}(NO_2)_2\text{-}2\text{-}MeC_6H_2CO]_2O$	94	2211
	*a*	CH_2Cl_2	Et_3N	20	0.5		96	2211
	*a*	CH_2Cl_2	N-EtPip	20	0.5		98	2211
	*c*	CH_2Cl_2	Et_3N	r.t.	1.5		92	2213

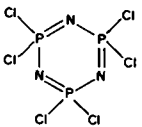
	*d*	CH_2Cl_2	Et_3N	r.t.	1		93	2213
	*a*	CH_2Cl_2	N-Et Pip	20	0.5		97	2211
Xanthene-9-carboxylic acid	*a*	CH_2Cl_2	Et_3N	20	1		98	2211
2-Fu COOH	*a*	CH_2Cl_2	Et_3N	20	0.5	$(2\text{-FuCO})_2O$	96	2211
1-Tetrazolylacetic acid	*a*	CH_2Cl_2	Et_3N	20	0.5	$(1\text{-Tetrazolyl } CH_2CO)_2O$	75	2211
3-PyrCOOH	*a*	THF	Et_3N	20	0.5	$(3\text{-Pyr } CO)_2O$	96	2211
	*a*	CH_2Cl_2	N-Et Pip	20	2.5		88	2211
	*a*	THF	N-Et Pip	20	0.6		99	2211

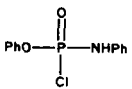
(*continued*)

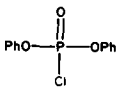
TABLE 109 (*continued*)

Substrate	Coupling agent	Solvent	Base	Temp. (°C)	Time (h)	Product	Yield (%)	References
Phthalimidoacetic acid	*a*	CH_2Cl_2	N-Et Pip	20	0.5	(Phthalimido $CH_2CO)_2O$	30	2211
Phthalimidoacetic acid	*c*	Me_2CO	Et_3N	r.t.	0.5	(Phthalimido $CH_2CO)_2O$	98	2213, 221[7]
Phthalimidoacetic acid	*d*	CH_2Cl_2	Et_3N	r.t.	0.25	(Phthalimido $CH_2CO)_2O$	92	2213
Phthalimidoacetic acid	Cl_3PO	CH_2Cl_2	C_5H_5N	r.t.	0.16	(Phthalimido $CH_2CO)_2O$	50	2214
Phthalimidoacetic acid	$PhOPOCl_2$	CH_2Cl_2	N-Et Pip	r.t.	0.16	(Phthalimido $CH_2CO)_2O$	40	2214
Phthalimidoacetic acid	$PhOPOCl_2$	CH_2Cl_2	C_5H_5N	r.t.	0.25	(Phthalimido $CH_2CO)_2O$	97	2214
Phthalimidoacetic acid	*f*	CH_2Cl_2	N-Et Pip	r.t.	0.5	(Phthalimido $CH_2CO)_2O$	40	2217
Phthalimidoacetic acid	*g*	CH_2Cl_2	N-Et Pip	r.t.	0.5	(Phthalimido $CH_2CO)_2O$	31	2217
(DL) Phthalimido CHMeCOOH	*c*	CH_2Cl_2	Et_3N	r.t.	0.5	(Phthalimido $CHMeCO)_2O$	95	2213
(DL) Phthalimido CHMeCOOH	*d*	CH_2Cl_2	Et_3N	r.t.	0.25	(Phthalimido $CHMeCO)_2O$	—	2213
(DL) Phthalimido CH(*i*-Pr)COOH	*c*	CH_2Cl_2	Et_3N	r.t.	0.5	[Phthalimido $CH(i\text{-Pr})CO]_2O$	98	2213
(DL) Phthalimido CH(*i*-Pr)COOH	*d*	CH_2Cl_2	Et_3N	r.t.	0.25	[Phthalimido $CH(i\text{-Pr})CO]_2O$	97	2213
$HOOC(CH_2)_2COOH$	*b*	CH_2Cl_2	Et_3N	−10 to 0	—	Succinic anhydride	—	2212
$HOOC(CH_2)_4COOH$	*a*	CH_2Cl_2	Et_3N	20	1	Polymeric	99	2211
HOOCCH=CHCOOH	*a*	CH_2Cl_2	Et_3N	20	1	Maleic anhydride	82	2211
Phthalic acid	*a*	CH_2Cl_2	Et_3N	20	1	Phthalic anhydride	98	2211
	*b*	CH_2Cl_2	Et_3N	−10 to 0	—		—	2212
Polyacrylic acid (Mr 150,000)	*b*	CH_2Cl_2, Et_2O	$(n\text{-Bu})_3N$	−10 to 0	—	Linear polyacrylic anhydride	75–90	2212

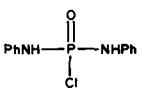
[a] *N,N*-Bis[2-oxo-3-oxazolidinyl]phosphorodiamide chloride 

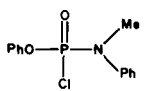
[b] 2,2,4,4,6,6-Hexachlorotriazatriphosphorine 

[c] Phenyl *N*-phenylphosphoramidochloridate 

[d] Diphenyl phosphorochloridate 

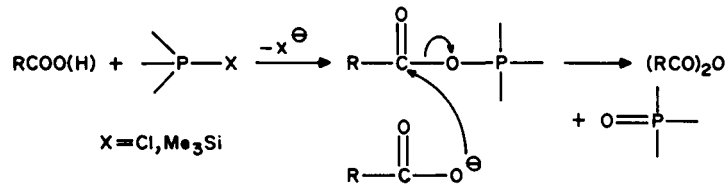
[e] PPSE = polyphosphoric acid trimethylsilyl ester reagent, a mixture of cyclotetraphosphate, isocyclotetraphosphate, linear tetraphosphate and a small amount of pyrophosphate. See Section VI.A.1 for structures.

[f] *N,N*-Diphenylphosphorodiamidochloridate 

[g] Phenyl *N*-methyl,*N*-phenylphosphoramidochloridate 

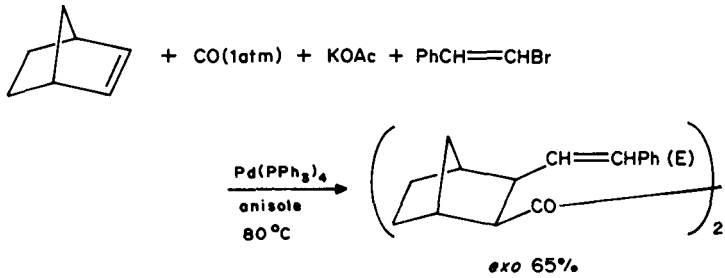
formation, several other phosphorous betaines were investigated[2210] using benzoic acid as the model substrate (equation 1176). The betaine formed from triphenylphosphine and DEAD produced the best results. The mechanism proposed[2210] for this condensation, regardless of the betaine employed, is shown in equation 1176.

The vast majority of phosphorous-containing condensing agents produce symmetrical acid anhydrides via the formation of an intermediate carboxylic acid–phosphoric acid mixed anhydride which undergoes nucleophilic attack by carboxylate anion to form the anhydride (equation 1177). The variety of reagents used and acid anhydrides produced are listed in Table 109.



(1177)

Phosphorous-containing catalysts have also been used in the preparation[2218] of strained symmetrical acid anhydrides by vinylation followed by carbonylation. Thus, reaction of bicyclo[2.2.1]hept-2-ene with (*E*)-β-bromostyrene in the presence of carbon monoxide, potassium acetate and tetra(triphenylphosphine) palladium produces[2218] the completely stereoselective *cis*, *exo*-anhydride by the mechanism shown in equation 1178.



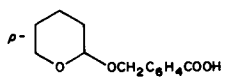
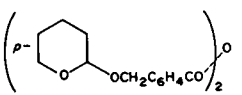
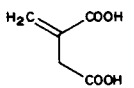
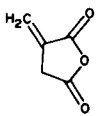
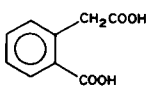
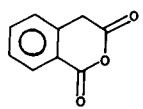
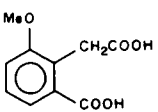
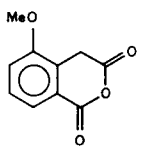
(1178)

In the series of silicon-containing coupling agents, (trimethylsilyl)ethoxyacetylene has been reported[2219] to be an excellent dehydrating agent for the synthesis of symmetrical acid anhydrides from carboxylic acids (equation 1179). Results are reported in Table 110.

The only recent examples of sulfur-containing coupling reagents reported have been sulfonyl chlorides, both alkyl and aryl. With these reagents the mechanism in each reaction involves the intermediate formation of a mixed sulfonic–carboxylic anhydride, which upon further reaction with a second equivalent of carboxylic acid produces the acid anhydrides (equation 1180). Utilizing this approach propanoic acid reacts with methanesulfonyl chloride in the presence of triethylamine to produce[2220] the corresponding carboxylic acid anhydride in 85% yield (equation 1181), while carboxylic acid amine salts react with tosyl chloride to produce[2221] the corresponding symmetrical carboxylic acid anhydride (equation 1182).

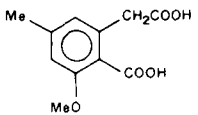
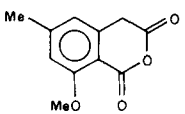
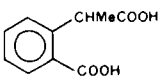
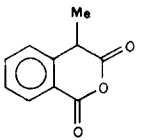
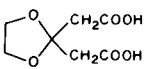
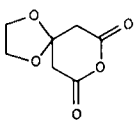
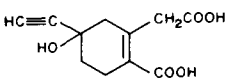
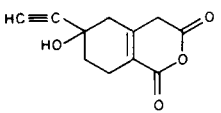
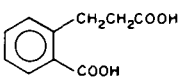
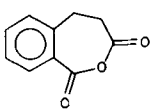
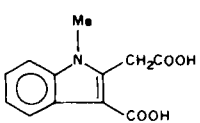
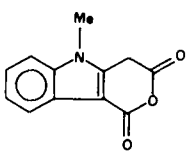
In at least one case[2222] the intermediate mixed sulfonic–carboxylic anhydride was isolated before reaction with a second equivalent of a different carboxylic acid to produce unsymmetrical carboxylic acid anhydrides (equation 1183).

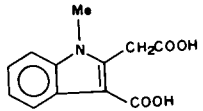
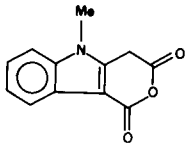
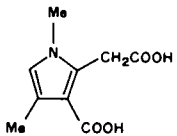
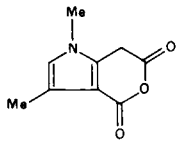
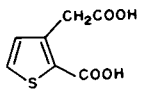
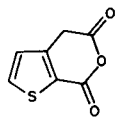
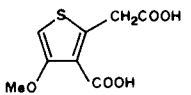
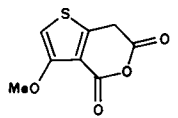
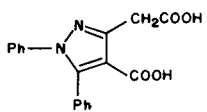
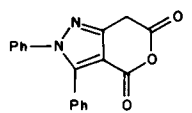
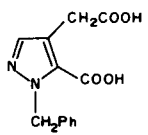
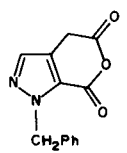
TABLE 110. Acid anhydrides prepared by using (trimethylsilyl)ethoxyacetylene[2219]

Acid	Solvent	Temp. (°C)	Time (h)	Product	Yield (%)
n-$C_{15}H_{31}COOH$	$Cl(CH_2)_2Cl$	60	2[a]	$(n\text{-}C_{15}H_{31}CO)_2O$	100
o-BrC_6H_4COOH	CH_2Cl_2	20	3	$(o\text{-}BrC_6H_4CO)_2O$	100
(E)-PhCH=CHCOOH	CH_2Cl_2	40	15	$[(E)\text{-PhCH=CHCO}]_2O$	96
p-$MeOCH_2OCH_2C_6H_4COOH$	CH_2Cl_2	40	10	$(p\text{-}MeOCH_2OCH_2C_6H_4CO)_2O$	100
p-$MeO(CH_2)_2(OCH_2)_2C_6H_4COOH$	CH_2Cl_2	40	11	$(p\text{-}MeO(CH_2)_2(OCH_2)_2C_6H_4CO)_2O$	100
	CH_2Cl_2	40	10		95
p-(t-Bu)$Me_2SiOCH_2C_6H_4COOH$	CH_2Cl_2	40	20	$[p\text{-}(t\text{-Bu})Me_2SiOCH_2C_6H_4CO]_2O$	100
Phenylsuccinic acid	CH_2Cl_2	40	5	Phenylsuccinic anhydride	100
	CH_2Cl_2	40	5		100
	CH_2Cl_2	20	7		100
	CH_2Cl_2	40	5		100

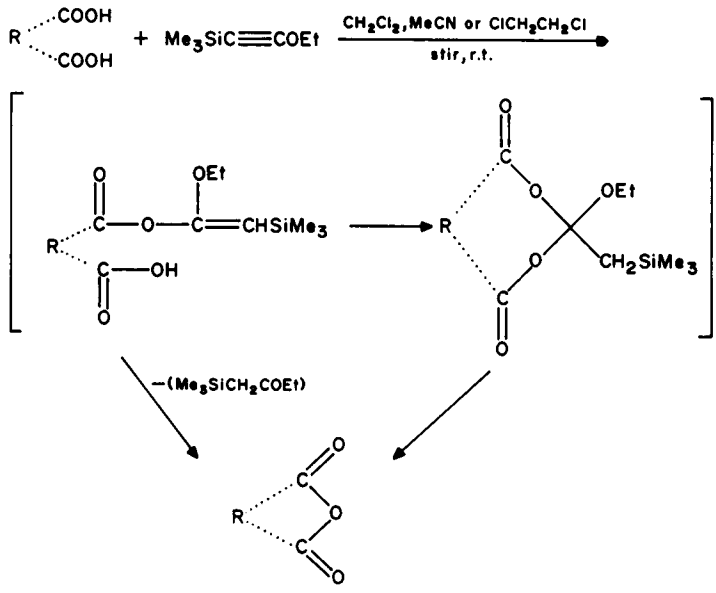
(*continued*)

TABLE 110 (*continued*)

Acid	Solvent	Temp. (°C)	Time (h)	Product	Yield (%)
	CH_2Cl_2	20	5		100
	CH_2Cl_2	20	3		100
	CH_2Cl_2	20	2		100
	$Cl(CH_2)_2Cl$	60	4		99
	CH_2Cl_2	40	15[a]		96
	$Cl(CH_2)_2Cl$/ THF (10:1)	60	3[a]		100

	MeCN	60	1[a]		100
	$Cl(CH_2)_2Cl$/ THF (10:1)	60	2.5[a]		90
	$Cl(CH_2)_2Cl$	60	1[a]		100
	$Cl(CH_2)_2Cl$	60	1[a]		85
	$Cl(CH_2)_2Cl$	60	1[a]		100
	$Cl(CH_2)_2Cl$/ THF (10:1)	60	6		86

[a]Days.



(1179)

$$R^1COOH + R^2SO_2Cl \xrightarrow{base} [R^2SO_2OCOR^1] \xrightarrow{R^3COOH} R^3{-}C(=O){-}O{-}C(=O){-}R^1 \quad (1180)$$

R^2 = alkyl or aryl; R^1 = or $\neq R^3$

$$EtCOOH + MeSO_2Cl \xrightarrow[-15\,^\circ C,\ N_2,\ 1\,h]{Et_3N,\ THF} (EtCO)_2O \quad (1181)$$

85%

$$RCOOH + NR_3 \xrightarrow[Me_2CO]{MeCN\ or} RCOO^{\ominus}\,\overset{+}{H}NR_3 \xrightarrow[20\text{–}30\,^\circ C]{p\text{-}MeC_6H_4SO_2Cl} (RCO)_2O \quad (1182)$$

Acid	Amine	Product	Yield (%)
PhCOOH	N-EtPip	$(PhCO)_2O$	52
p-ClC_6H_4COOH	N-EtPip	$(p\text{-}ClC_6H_4CO)_2O$	100
p-BrC_6H_4COOH	N-EtPip	$(p\text{-}BrC_6H_4CO)_2O$	89
p-$O_2NC_6H_4COOH$	Et_3N	$(p\text{-}O_2NC_6H_4CO)_2O$	100
$PhCH_2COOH$	N-EtPip	$(PhCH_2CO)_2O$	54
PhCH=CHCOOH	N-EtPip	(PhCH=CHCO)$_2$O	68
Phthalic acid	N-EtPip	Phthalic anhydride	76
$HOOC(CH_2)_4COOH$	Et_3N	$(HOOC(CH_2)_4CO)_2O$	80

$$RSO_2Cl + R^1COOH \xrightarrow[\text{dioxane, } <0\,^\circ C]{Et_3N \text{ or } C_5H_5N,} RSO_2OCOR^1 \xrightarrow[0\,^\circ C]{R^2COOH} R^1{-}\overset{O}{\overset{\|}{C}}{-}O{-}\overset{O}{\overset{\|}{C}}{-}R^2$$

39–72% 35–63%

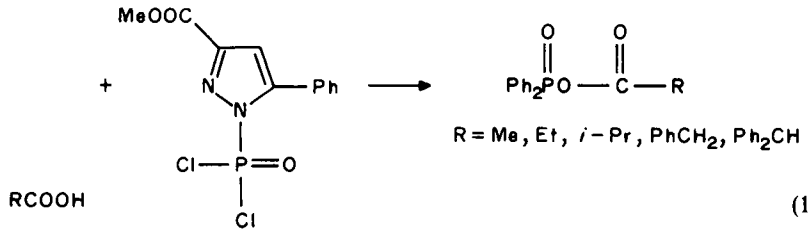
(1183)

R = Ph, *p*-Tol
R^1 = Et, Ph, *p*-$O_2NC_6H_4$
R^2 = $PhCH_2$, *o*-Tol, *p*-$O_2NC_6H_4$

Other mixed inorganic–carboxylic anhydrides which have been prepared and isolated, but which have not been used to produce carboxylic acid anhydrides, include sulfonic–carboxylic anhydrides[2223] (equation 1184), diphenyl-[2224] (equation 1185) and dihalophosphoric–carboxylic anhydride[2225]. In the latter case the starting materials used were not the organic and the inorganic acids, but the corresponding symmetrical acid anhydrides of each. Thus this reaction is a sort of inorganic–organic anhydride interchange (equation 1186).

$$RCOOH + MeSO_2Cl \xrightarrow{C_5H_5N} R{-}\overset{O}{\overset{\|}{C}}{-}OSO_2Me \qquad (1184)$$

R = *m*-$O_2NC_6H_4$, *p*-An, *p*-ClC_6H_4, (*Z*)-PhCH=CH, *n*-$C_{17}H_{35}$, 2- and 4-carbomethoxynicotinyl.



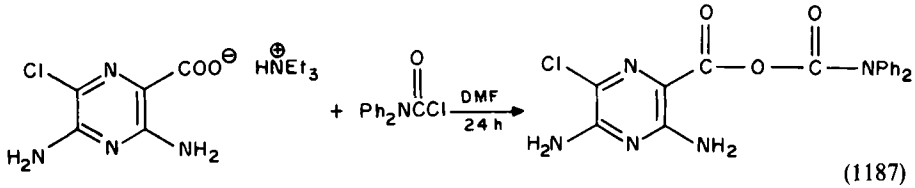
(1185)

$$(RCO)_2O + (X_2P)_2O \xrightarrow[8\,h]{95\,^\circ C} R{-}\overset{O}{\overset{\|}{C}}{-}O{-}\overset{O}{\overset{\|}{P}}X_2 \qquad (1186)$$

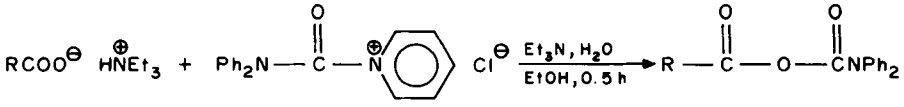
60–90%

R = Me, Ph, *p*-Tol
X = Cl, F

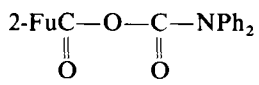
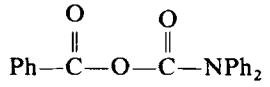
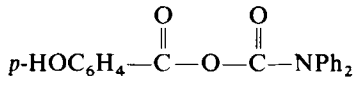
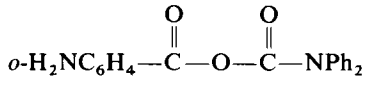
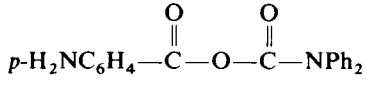
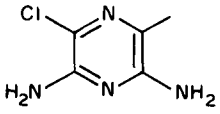
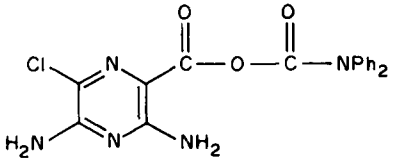
Other mixed anhydrides which appear in the recent literature include: carboxylic-*N*,*N*-diphenylcarbamic anhydrides[2226], prepared by the reaction of the triethylammonium salts of the carboxylic acid with either diphenylcarbamoyl chloride (equation 1187) or with (1,1-diphenylcarbamoyl)pyridinium chloride (equation 1188); carboxylic–pyridyloxy anhydrides[2227], prepared by the reaction of 2-pyridyl chloroformate with a carboxylic acid in the presence of triethylamine (equation 1189); and carboxylic-*N*-carbonyl-2-pyrrolidinonyl anhydrides[2228], prepared by the reaction of *N*-chlorocarbonyl-2-pyrrolidinone with 6-phenoxyacetamidopenicillanic acid (equation 1190).



(1187)

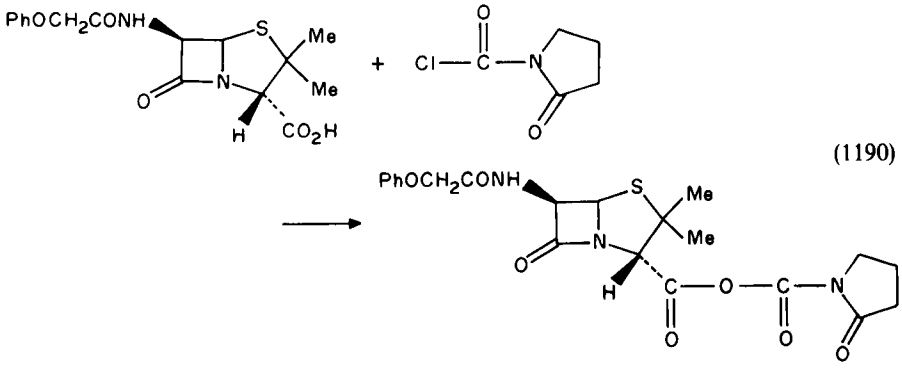


(1188)

R	Product
2-Fu	
Ph	
p-HOC_6H_4	
o-$H_2NC_6H_4$	
p-$H_2NC_6H_4$	
	

$$\text{2-PyrOCOCl} + \text{RCOOH} \xrightarrow[0\,^\circ\text{C, 30 min}]{\text{Et}_3\text{N, CH}_2\text{Cl}_2} \text{2-PyrOCOOCOR} \quad (1189)$$

R = *n*-Pr, *i*-Pr, *t*-Bu, Ph, $PhCOCH_2CH_2$, $MeOOC(CH_2)_4$, $Br(CH_2)_5$, PhCH=CH, mesitoic



(1190)

*V. SYNTHESIS OF ACYL HALIDES

At least one review[2229] on the synthesis of acid chlorides of aliphatic carboxylic acids has appeared in the recent literature.

*A. From Carboxylic Acids and Anhydrides

Carboxylic acids and anhydrides have been converted into acyl halides using several different classes of reagents including carbon, nitrogen, phosphorous, sulfur and other reagents. This statement defines the format and order which will be used to present the material in this section.

Oxalyl chloride[2230] and phosgene[2231,2232] have been used recently to prepare acyl chlorides from carboxylic acids. Reaction of α,β-unsaturated β-fluorocarboxylic acids with oxalyl chloride produced[2230] isomeric mixtures of the corresponding acyl chlorides (equation 1191), while reaction of phosgene with aliphatic monocarboxylic acids[2231] and aromatic dicarboxylic acids[2231,2232] produced the corresponding mono- or diacyl chlorides (equation 1192).

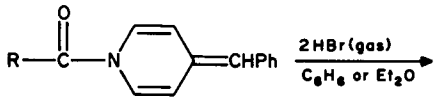
$$\text{RCF=CHCOOH} + (\text{COCl})_2 \xrightarrow[20\,^\circ\text{C, 2 h}]{\text{CH}_2\text{Cl}_2} \text{RCF=CHCOCl} \quad (1191)$$

	R = *n*-Bu	Ph
Yield (%) =	80	60
E/Z ratio =	87/13	85/15

$$\text{RCOOH} + \text{COCl}_2 \xrightarrow{\text{conditions}} \text{RCOCl} \quad (1192)$$

Acid	Conditions	Product	Reference
$ClCH_2CH_2COOH$	DMF, PhMe, 70 °C, 5 h	$ClCH_2CH_2COCl$	2231
1,4-$(COOH)_2C_6H_4$	DMF, PhMe, 70 °C, 5 h	1,4-$(COCl)_2C_6H_4$	2231
1,3-$(COOH)_2C_6H_4$	DMF, PhMe, 70 °C, 5 h	1,3-$(COCl)_2C_6H_4$	2231
1,3-$(COOH)_2C_6H_4$	DMF, PhCl, 60–65 °C, stir, 3 h	1,3-$(COCl)_2C_6H_4$	2232

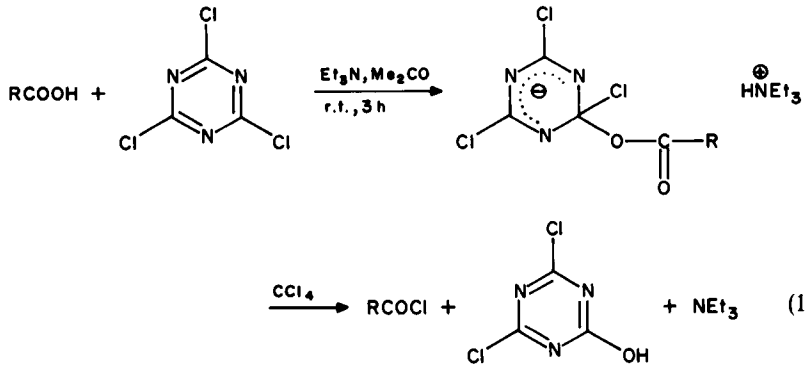
Nitrogen-containing reagents have been used to prepare acyl bromides, chlorides, fluorides and iodides from carboxylic acids. Thus, reaction of 1-acyl-4-benzylidene-1,4-dihydropyridine with gaseous hydrogen bromide in benzene or ether solvent affords[2233] acyl bromides in excellent yields (equation 1193).



(1193)

R = Me	PhCH=CHPh	Ph	*p*-Tol	*p*-An
Yield (%) = 71	95	98	98	100
Solvent = Et_2O	C_6H_6	C_6H_6	C_6H_6	C_6H_6

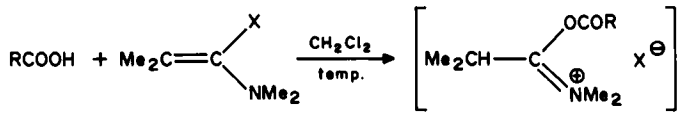
Treatment of carboxylic acids with cyanuric chloride in the presence of triethylamine in acetone solvent produces[2234,2235] an insoluable hydroxydichloro-*S*-triazine intermediate, which when dissolved in carbon tetrachloride followed by concentration of the resulting solution affords the acyl chlorides (equation 1194), albeit in poor yields.



(1194)

Acid	Product	Yield (%)	Reference
HCOOH	HCOCl	Not isolated	2234
n-$C_{17}H_{35}COOH$	n-$C_{17}H_{35}COCl$	Not isolated	2234
Cl_3CCOOH	Cl_3CCOCl	40	2234
F_3CCOOH	F_3CCOCl	Not isolated	2234
$Ph_2CHCOOH$	$Ph_2CHCOCl$	32	2234
PhCOOH	PhCOCl	81	2235
p-$O_2NC_6H_4COOH$	p-$O_2NC_6H_4COCl$	58	2234, 2235
4-PyrCOOH	4-PyrCOCl	21	2234
$CH_2=CH(CH_2)_8COOH$	$CH_2=CH(CH_2)_8COCl$	Not isolated	2234
$CH_2(COOH)_2$	$CH_2(COCl)_2$	Not isolated	2234
1,2-$(COOH)_2$-3-$(NO_2)C_6H_3$	1,2-$(COCl)_2$-3-$(NO_2)C_6H_3$	36	2234

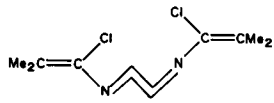
By reaction of carboxylic acids with tetramethyl-α-halogenoenamines all halide representatives of the acyl halides can be prepared[2236] in excellent to quantitative yields (equation 1195) essentially instantaneously.



(1195)

R	X	Temp. (°C)	Yield (%)
H	F	−30(1h)	100
H	Cl	−60	94[a]
H	Br	0	100
H	I	−20	100
Me	I	20	100
t-Bu	F	20	100
t-Bu	Cl	20	100
t-Bu	Cl	20	70[b]
t-Bu	Br	20	100
t-Bu	I	20	100
Cl_2CH	F	20	98
Cl_3C	F	20	100
Cl_3C	Cl	20	100
N_2CH	Cl	−10(3h)	100
	Cl	20	100
$(MeO)_2CH$	Cl	−40(1h)	94
$CH_2=CH$	Cl	20	96
$CH_2=CH$	Br	20	100
MeCH=CMe	F	20	97
2-Pyrrolyl	Cl	20	100
2-Fu	Cl	20	100
Ph	F	20	100
Ph	I	20	100
HCO	Cl	−20	96[a]
MeCO	Cl	−20(4h)	100[a]
PhCO	Cl	0	80[c]
$HOOCCH_2$	Cl	20	100[d]

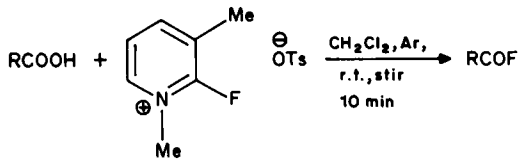
[a] Isolated as methyl ester.

[b] Using  as reagent.

[c] Isolated as anilide.

[d] Product isolated was $CH_2(COCl)_2$.

Various carboxylic acid fluorides have been prepared[2237] in good to excellent yields by treating carboxylic acids with 2-fluoro-1,3-dimethylpyridinium tosylate and triethylamine at room temperature (equation 1196).



(1196)

R	Yield (%)	R	Yield (%)
n-Pen	84	MeCH=CH	64
n-$C_{11}H_{23}$	100	Me(CH=CH)$_2$	89
$PhCH_2$	80	PhCH=CH	69
$PhCH_2CH_2$	88	Ph	93
PhCHEt	87	$HOOC(CH_2)_5$	93[a]
PhCH(OMe)	87		

[a]Product was $FOC(CH_2)_5COF$.

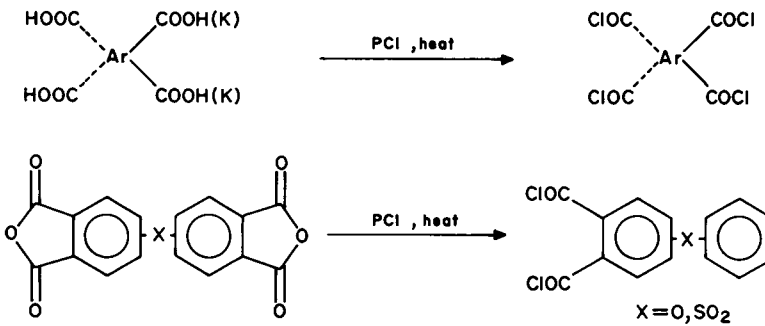
Phosphorous pentachloride is the simplest member of the series of phosphorous-containing reagents which have been used to prepare acyl chlorides from carboxylic acids and anhydrides. In one recent report[2238] polymer-bonded phosphorous pentachloride, prepared by reacting Amberlite IRA 93, a macroporous styrene–divinylbenzene copolymers functionalized with tertiary amine groups with phosphorous petachloride in carbon tetrachloride, reacted with carboxylic acids under reflux to produce the corresponding acyl chlorides (equation 1197).

$$\text{Resin-}CH_2NR_2\cdot PCl_5 + RCOOH \xrightarrow[\text{reflux}]{\text{solvent}} RCOCl \quad \text{(Amberlite IRA 93)} \tag{1197}$$

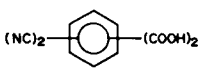
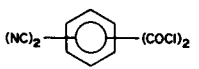
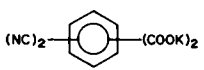
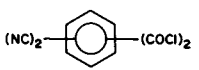
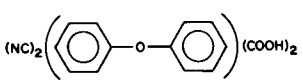
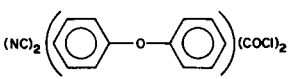
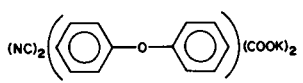
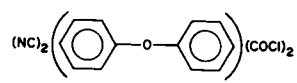
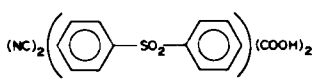
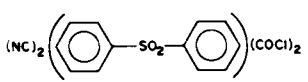
R	Solvent	Time (h)	Yield (%)
n-C_9H_{19}	$ClCH_2CH_2Cl$	2	86
$MeOOC(CH_2)_7$	$ClCH_2CH_2Cl$	2	73
Ph_2CH	CH_2Cl_2	6	68
c-Hex	CH_2Cl_2	6	80
MeCH=CH	CH_2Cl_2	6	51
PhCH=CH	$ClCH_2CH_2Cl$	2	91
Ph	CH_2Cl_2	6	75
1,3,5-$Me_3C_6H_2$	$ClCH_2CH_2Cl$	6	71
$HOOC(CH_2)_2$	$ClCH_2CH_2Cl$	6	48[a]

[a]Product was $ClOC(CH_2)_2COCl$.

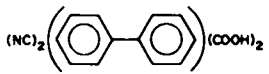
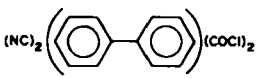
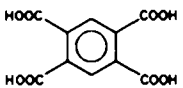
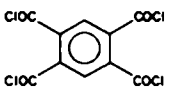
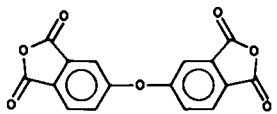
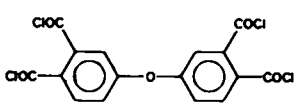
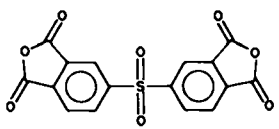
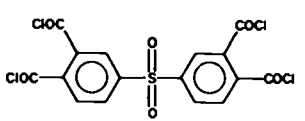
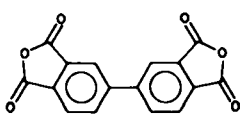
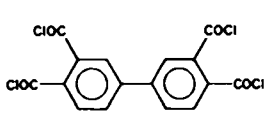
Neat phosphorous pentachloride has also been used[2239] to convert di- and tetracarboxylic acids, their potassium salts and their anhydrides into the corresponding di- and tetraacyl chlorides (equation 1198).



(1198)

Substrate	Solvent	Temp. (°C)	Time (h)	Product	Yield (%)
	CCl_4	50–60	2.5		53[a]
	CCl_4	—	4		62[a]
	CCl_4	50–60	2.5		50[a]
	CCl_4	—	4		55[a]
	CCl_4	50–60	2.5		27[a]

(*continued*)

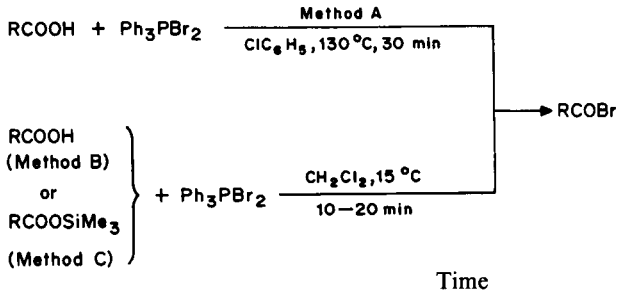
Substrate	Solvent	Temp. (°C)	Time (h)	Product	Yield (%)
	CCl_4	50–60	2.5		25[a]
	—	175	—		60
	—	175	22		66
	—	175	12		50
	—	175	8		57

[a]Location of CN and COOH or COCl groups in relation to each other on aromatic rings are unspecified.

Dropwise addition of dimethylformamide to a solution of perfluorobutanoic acid and phosphorous oxychloride produces[2240] the corresponding perfluoroacyl chloride in 96.8% yield (equation 1199).

$$F_3CCF_2CF_2COOH + POCl_3 \xrightarrow{DMF} F_3CCF_2CF_2COCl \qquad (1199)$$

Using triphenylphosphine dibromide, three methods have been employed[2241] to produce acyl bromides. In method A the carboxylic acid and the dibromide are refluxed in chlorobenzene (equation 1200), in method B the same two reagents are used in methylene chloride at 15 °C (equation 1200) and method C utilizes the trimethylsilyl ester of the carboxylic acids (equation 1200).



(1200)

Substrate	Method	Time (min)	Yield (%)
EtCOOH	A	30	65
EtCOOH	B	15	84
$PhCH_2CH_2COOH$	A	30	80
$PhCH_2CH_2COOSiMe_3$	C	15	70
$Me_2C{=}CHCOOH$	A	30	50
$Me_2C{=}CHCOOSiMe_3$	C	15	91
$PhCH{=}CHCOOH$	A	30	76
$PhCH{=}CHCOOSiMe_3$	C	10	90
PhCOOH	A	30	72
PhCOOH	B	15	90
o-ClC_6H_4COOH	B	15	64
o-$ClC_6H_4COOSiMe_3$	C	15	77
p-ClC_6H_4COOH	B	15	81
$PhCH(COOH)_2$	A	30	*a*
$PhCH(COOH)_2$	B	10	89
$PhCH(COOSiMe_3)_2$	C	15	90

[a] Product formed was $PhCH_2COBr$.

Also reported in the same reference[2241] is the preparation of acyl bromides as unisolated intermediate which are used *in situ* to prepare esters with trimethylsilyl ethers (equation 1201).

$$R^1COOSiMe_3 + Ph_3PBr_2 \xrightarrow[10\text{–}20\,min]{CH_2Cl_2,\ 15\,°C} [R^1COBr] \xrightarrow{R^2OSiMe_3} R^1COOR^2 \qquad (1201)$$

R^1 = Et; $PhCH_2CH_2$; $H_2C{=}CMe$; $MeCH{=}CH$; $Me_2C{=}CH$; $PhCH{=}CH$; Ph; 3,5-$(O_2N)_2C_6H_3$ and $PhCH(CO{-}{-})_2$

The intermediate formation of acyl chlorides which were used directly without isolation to produce esters[2242,2243] and amides[2243] has also been reported.

In the series of sulfur-containing reagents only two representatives have been reported in the recent literature. Sulfur monochloride in the presence of an iron salt catalyst has been used[2244] to convert mono- and dicarboxylic acids into their corresponding mono- and diacyl chlorides (equation 1202).

$$\text{RCOOH} + \text{S}_2\text{Cl}_2 \xrightarrow[\text{catalyst}]{\text{Cl}_2,\ \text{iron salt}} \underset{70\text{–}96\%}{\text{RCOCl}} \qquad (1202)$$

R = Me, Et, *n*-Pr, *n*-Bu, Ph, *p*-$O_2NC_6H_4$, *p*-$HO_2CC_6H_4$[a], *m*-$HO_2CC_6H_4$[a], $HO_2C(CH_2)_4$[a]

[a] Products were diacyl chlorides.

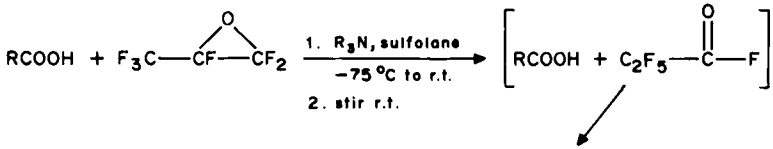
By far the most popular sulfur-containing reagent used continues to be thionyl chloride. Table 111 lists the carboxylic acids used and products formed, including the acyl chlorides which were not isolated but were used directly to produce other functional groups. The general reaction for these conversions is shown in equation 1203.

$$\text{RCOOH} + \text{SOCl}_2 \longrightarrow \text{RCOCl} \qquad (1203)$$

Two recent reports describe the preparation of acyl fluorides from carboxylic acids using reagents that have not already been discussed. Thus, reaction of carboxylic acids with sulfur tetrafluoride[2251] (equation 1204) or with hexafluoro-1,2-epoxypropane[2252] (equation 1205) produces the corresponding acyl fluorides.

$$\text{RCOOH} + \text{SF}_4 \longrightarrow \text{RCOF} \qquad (1204)$$

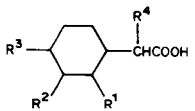
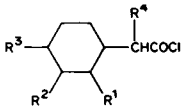
R = Me, *n*-Pr, *i*-Pr, *n*-Bu, *t*-Bu, *n*-Pen, $MeCOCH_2$, *c*-Hex, $BrCH_2$, Cl_2CH, Cl_3C, MeCHCl, $ClCH_2CH_2$, *c*-C_3H_5, Ph



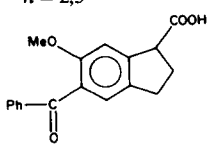
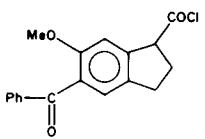
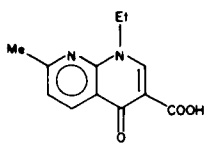
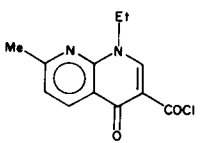
(1205)

Acid	NR_3	Time (min)	Yield (%)
EtCOOH	$PhNMe_2$	90	86
i-PrCOOH	$PhNMe_2$	90	87
n-$C_7H_{15}COOH$	Et_3N	30	89
PhCOOH	Et_3N	30	79
p-TolCOOH	Et_3N	60	77

TABLE 111. Acyl chlorides produced using thionyl chloride

Acid	Solvent	Conditions	Product	Yield (%)	Reference
$RCMe_2COOH$ R = *n*-alkyl C_1–C_6	—	Reflux	$RCMe_2COCl$	80–90	2245
RCMeEtCOOH R = *n*-alkyl C_2–C_5	—	Reflux	RCMeEtCOCl	80–90	2245
$RN(NO_2)CH_2CH_2COOH$ R = Me, Et	$CHCl_3$	Reflux, 2 h	$RN(NO_2)CH_2CH_2COCl$	90	2246
	C_6H_6	Reflux, 4 h		Not isolated	2247

R^1	R^2	R^3	R^4
Me	H	H	Me
Me	H	H	Et
Me	H	H	*i*-Pr
Me	H	H	$CH_2{=}CHCH_2$
Me	H	H	$PhCH_2$
H	Me	Me	Me
H	Me	Me	Et

$p\text{-}F_3C(CH_2)_nC_6H_4COOH$ *n* = 2,3	C_5H_5N	Reflux, 3 h	$p\text{-}F_3C(CH_2)_nC_6H_4COCl$	Not isolated	2248
	—	Heat		—	2249
	$CHCl_3$	Reflux		—	2250

***B. From Esters**

By using a mixture of phthaloyl chloride and chlorosulfonic acid, ethyl esters of carboxylic acids have been converted[2253] in one step to acyl chlorides (equation 1206).

$$RCOOEt + 1,2\text{-}(COCl)_2C_6H_4 \xrightarrow[\text{heat}]{ClSO_2OH} RCOCl \qquad (1206)$$

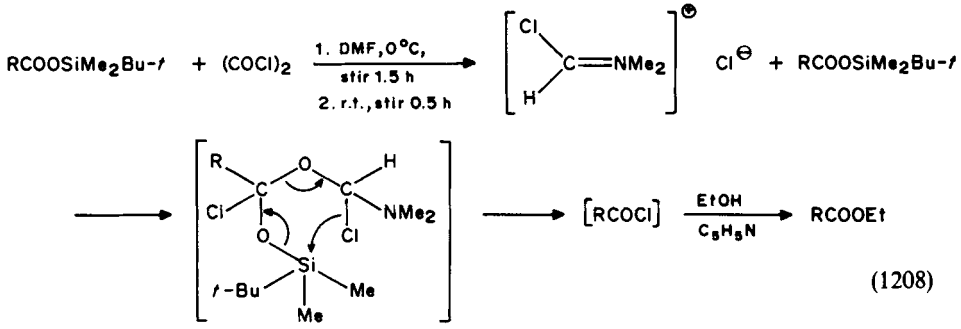
R =	FCHCl	FCHCl	FCHBr	$ClCH_2$	Me	$CF_3(CH_2)_2$
Yield =	88	50[a]	62	—	52	0[b]

[a] Reaction was run using only chlorosulfonic acid.
[b] No acyl chloride was obtained, only the carboxylic acid was isolated.

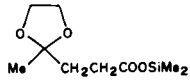
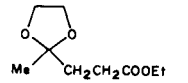
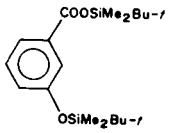
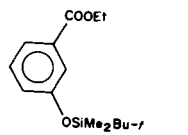
The most common carboxylic acid esters used as starting materials in the preparation of acyl halides have been silyl esters, as illustrated by the reaction[2254] of trimethylsilyl acetate with the antimony hexafluoride salt of [(1,1,7-trihydrododecafluoroheptyl)-oxy] trifluorosulfurane (equation 1207).

$$MeCOOSiMe_3 + F_3C(CF_2)_5O\overset{\oplus}{S}F_2Sb^{\ominus}F_6 \xrightarrow[-20\,^\circ C]{\text{Freon 113}} \underset{98\%}{MeCOF} \qquad (1207)$$

Another series of silyl esters which have been converted to acyl halides are the *t*-butyldimethylsilyl esters of carboxylic acids. By reaction of these esters with oxalyl chloride in the presence of DMF, the resulting acyl chlorides were produced[2255] *in situ*, and directly converted to their corresponding ethyl esters by reaction with ethanol in pyridine (equation 1208).



(1208)

Starting esters	Product esters	Yield (%)
$Me(CH_2)_5COOSiMe_2Bu\text{-}t$	$Me(CH_2)_5COOEt$	92
		95
$t\text{-}BuMe_2SiOCH_2COOSiMe_2Bu\text{-}t$	$t\text{-}BuMe_2SiOCH_2COOEt$	87
		98

Similar *t*-butyldimethylsilyl esters have also been converted to acyl bromides by reaction[2256] with triphenylphosphine dibromide in methylene chloride. These acyl bromides were also produced *in situ* and most were directly converted to and isolated as a derivative of the carboxylic acid (equation 1209).

$$R^1COOSiMe_2Bu\text{-}t + Ph_3PBr_2 \xrightarrow[\text{r.t.}]{CH_2Cl_2} [R^1COBr] \qquad (1209)$$

$[R^1COBr]$ + R^2OH → R^1COOR^2

$[R^1COBr]$ + $PhNH_2$ → $R^1CONHPh$

Starting ester	Time	Product	Yield (%)
$PhCH_2COOSiMe_2(Bu\text{-}t)$	15 min	$PhCH_2COBr$	91
$Ph_2CHCOOSiMe_2(Bu\text{-}t)$	40 min	$Ph_2CHCOOMe$	84
$t\text{-}BuCCOOSiMe_2(Bu\text{-}t)$	25 min	$t\text{-}BuCCONHPh$	76
$t\text{-}BuCOOSiMe_2(Bu\text{-}t)$	3 min[a]	$t\text{-}BuCCONHPh$	80
$CH_2{=}CMeCOOSiMe_2Bu\text{-}t$	30 min	$CH_2{=}CMeCOOEt$	84
$(Z)\text{-}Me(CH_2)_7CH{=}CH(CH_2)_7COOSiMe_2Bu\text{-}t$	30 min	$Me(CH_2)_7CH{=}CH(CH_2)_7COBr$	90
$Me_2C{=}CHCOOSiMe_2Bu\text{-}t$	20 min	$Me_2C{=}CHCOBr$	90
$(E)\text{-}PhCH{=}CHCOOSiMe_2Bu\text{-}t$	30 min	$PhCH{=}CHCOOEt$	97
$PhCOOSiMe_2Bu\text{-}t$	25 h	PhCOOMe	89
$PhCOOSiMe_2Bu\text{-}t$	20 min[a]	PhCOOMe	85
$o\text{-}TolCOOSiMe_2Bu\text{-}t$	1.5 h	$o\text{-}TolCONHPh$	90
$p\text{-}ClC_6H_4COOSiMe_2Bu\text{-}t$	3.5 h	$p\text{-}ClC_6H_4COBr$	91
$p\text{-}ClC_6H_4COOSiMe_2Bu\text{-}t$	1 h[a]	$p\text{-}ClC_6H_4COBr$	92
$p\text{-}O_2NC_6H_4COOSiMe_2Bu\text{-}t$	6 h	$p\text{-}O_2NC_6H_4COOEt$	90
$p\text{-}O_2NC_6H_4COOSiMe_2Bu\text{-}t$	75 min[a]	$p\text{-}O_2NC_6H_4COOEt$	87
$2,4,6\text{-}Me_3C_6H_2COOSiMe_2Bu\text{-}t$	15 min	$2,4,6\text{-}Me_3C_6H_2COOEt$	99
$PhCHOSiMe_2Bu\text{-}t$ | $COOSiMe_2Bu\text{-}t$	15 min	$PhCHOSiMe_2Bu\text{-}t$ | $COOEt$	70
$N{\equiv}CCH_2COOSiMe_2Bu\text{-}t$	30 min	$N{\equiv}CCH_2COOCH_2Ph$	75
$PhCONHCH_2COOSiMe_2Bu\text{-}t$	15 min	$PhCONHCH_2COOEt$	90
$MeOCH_2COOSiMe_2Bu\text{-}t$	10 min	$MeOCH_2COOEt$	92

[a] $ZnBr_2$ added.

*C. From Trihalides

The preparation of acid chlorides from trihalides[2257] involves the reaction of chloropolyfluorides with sulfuric acid in the presence of mercuric oxide. This produces the carboxylic acid by hydrolysis, followed by treatment with thionyl chloride to produce the corresponding acid chloride (equation 1210).

$$Cl(CFCl{-}CF_2)_3CCl_3 \xrightarrow[\text{2. } SOCl_2, PhCOCl]{\text{1. } H_2SO_4, HgO} Cl(CFCl{-}CF_2)_3COCl \qquad (1210)$$

*E. Miscellaneous Methods

Reaction of perfluoroalkyl iodides with a metal couple and sulfur dioxide in DMSO followed by treatment with chlorine in methanol produces[2258] perfluoroalkanesulfonyl chlorides in yields ranging from 40 to 80% (equation 1211). The mechanism is reported to

involve formation of the perfluoroalkylzinc iodide on the surface of the other metal used in the couple, followed by insertion of the sulfur dioxide into the organometallic reagent. The intermediate salt produced then reacts with chlorine to produce the sulfonyl chloride (equation 1212).

$$R_FI + \text{metal couple} + SO_2(g) \xrightarrow[2.\ Cl_2(g),\ MeOH]{1.\ DMSO} R_FSO_2Cl \qquad (1211)$$

metal couples used: Pd–Zn, Cd–Zn, Hg–Zn or Zn–Cu

$$R_FI + Zn\text{-}M \rightarrow R_FZnI \text{ on M surface} \xrightarrow{SO_2} R_FSO_2ZnI \xrightarrow{Cl_2} R_FSO_2Cl \qquad (1212)$$

R_FI	Conditions[a]	Yield (%)[b]
n-C_4F_9I	25 °C, 3 h	40
n-C_4F_9I	30 °C, 2 h	55
n-$C_6F_{13}I$	25 °C, 3 h	40
n-$C_6F_{13}I$	45 °C, 4 h	80
n-$C_8F_{17}I$	25 °C, 3 h	52
n-$C_8F_{17}I$	45 °C, 2 h	75

[a] Mole ratio of Zn–Cu couple to $R_FI = 1.5:1$.
[b] Based upon R_FI consumed.

Sequential α-bromination, then acid chloride production from carboxylic acids has been accomplished[2259] in the presence of the anhydride of the carboxylic acid using bromine and boron tribromide followed by treatment with chlorine and hydrogen chloride (equation 1213).

$$MeCOOH + (MeCO)_2O \xrightarrow[2.\ Cl_2,\ HCl]{1.\ Br_2,\ BBr_3} BrCH_2COCl \qquad (1213)$$

*VI. SYNTHESIS OF AMIDES

*A. Amides by Acylation Reactions

*1. Acylation with carboxylic acids

The reaction of carboxylic acids with amines to form amides is a fundamental reaction in synthetic organic chemistry and several reviews of this reaction have appeared[2260–2265].

Reactions of carboxylic acids or their salts with amines in the presence of condensing agents, as compared to the direct thermolysis of ammonium carboxylates, continues to be the method of choice for the preparation of amides. The condensing agents used in these reactions range from boron to organotin reagents and include nitrogen- and phosphorous-containing reagents. This section reports the reactions of carboxylic acids with amines in essentially alphabetic order based upon the condensing agent used.

Treatment of carboxylic acids with amines in the presence of boron trifluoride etherate and triethylamine affords the corresponding amides in yields ranging from 28 to 100 percent (equation 1214).

$$R^1COOH + R^2R^3NH \xrightarrow[\text{solvent}]{BF_3\cdot Et_2O,\,Et_3N} R^1CONR^2R^3 \qquad (1214)$$

R^1	R^2	R^3	Time (h)	Solvent	Yield (%)
n-Bu	$PhCH_2$	H	100	C_6H_6	100
PhCH=CH	$PhCH_2$	H	66	C_6H_6	63
Ph	*n*-Bu	H	100	C_6H_6	76
Ph	$-(CH_2)_5-$		50	MeC_6H_5	63
Ph	$PhCH_2$	H	100	C_6H_6	83
Ph	$PhCH_2$	H	22	C_6H_6[a]	86
Ph	$Et_2NCH_2CH_2$	H	22	C_6H_6	82
Ph	Ph	H	100	MeC_6H_5	28
p-$H_2NC_6H_4$	$Et_2NCH_2CH_2$	H	22	C_6H_6	64
p-$H_2NC_6H_4$	$Et_2NCH_2CH_2$	H	70	C_6H_6	94
o-$H_2NC_6H_4$	$Et_2NCH_2CH_2$	H	43	C_6H_6	28
m-ClC_6H_4	$Et_2NCH_2CH_2$	H	22	C_6H_6	73
p-$O_2NC_6H_4$	$Et_2NCH_2CH_2$	H	22	C_6H_6	45

[a]Sodium benzoate was used as a base instead of triethylamine.

Reaction of carboxylic acids with benzonitrile in the presence of iron(II) chloride produces[2266,2267] iron(II)-coordinated amides of the carboxylic acids (equation 1215).

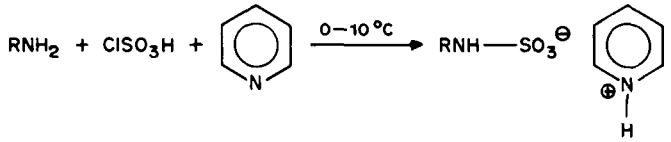
$$RCOOH + PhCN + FeCl_2 \quad (\text{mole ratio} = 7\text{–}10{:}2{:}1;\ R = C_1\text{–}C_6,\ n\text{-alkyl}) \qquad (1215)$$

- $\xrightarrow{110\,^\circ C}$ $FeCl_2\cdot PhCONH_2 + FeCl_2\cdot PhCONHCOR$ (60–75% and 90–92%; R = Me or Et)
- $\xrightarrow{130\text{–}170\,^\circ C}$ $FeCl_2\cdot(RCO)_2NH$ (80–90%; R = *n*-Pr, *n*-Bu, *n*-Pen)

Nitrogen-containing reagents which have been used as condensing agents in recent literature reports include dicyclohexylcarbodiimide (DCCD), which catalyzes the condensation of ω-(acyl)aminoalkanoic acids or their salts with ω-aminomercaptans and disulfides to produce carboxamides[2268]. One example of this reaction is illustrated in equation 1216.

$$HCONHCH_2CH_2C\overset{\ominus}{O}O\overset{\oplus}{N}a + (H_2NCH_2CH_2S)_2 \xrightarrow[\substack{H_2SO_4,\,DCCD\\ r.t.,\,2\,days}]{H_2O,\,C_5H_5N} HCONHCH_2CH_2CONHCH_2CH_2S]_2 \quad (62.2\%) \qquad (1216)$$

Pyridinium salts of sulfamic acid, prepared by reaction of a primary amine and pyridine with chlorosulfonic acid (equation 1217), have been reported[2269] to react with carboxylic acids via a four-centered transition state to produce the corresponding amides (equation 1218).



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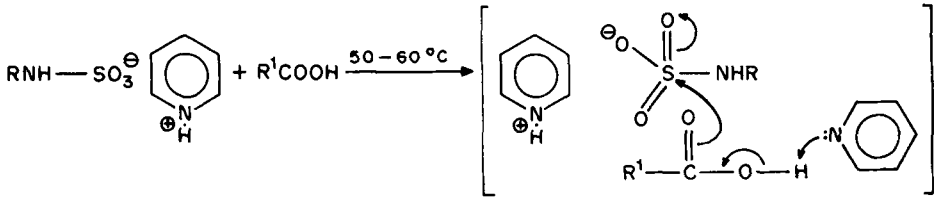
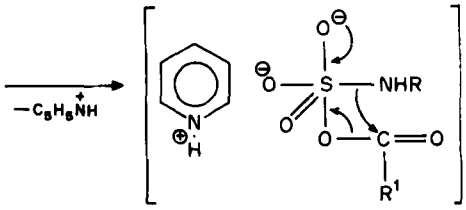


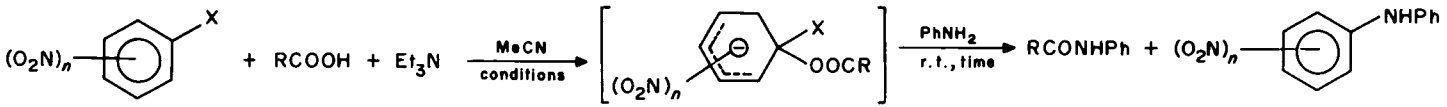


(1218)

Amine	Acid	Amide	Yield-(%)[c]
$PhNH_2$	MeCOOH[a]	MeCONHPh	71
p-$TolNH_2$	MeCOOH[a]	$MeCONHC_6H_4Me$-*p*	77
p-$O_2NC_6H_4NH_2$	MeCOOH[a]	$MeCONHC_6H_4NO_2$-*p*	64[d]
2-$NaphNH_2$	MeCOOH[a]	2-NaphNHCOMe	73
$PhNH_2$	$PhCH_2COOH$[a]	$PhCH_2CONHPh$	78
p-$TolNH_2$	$PhCH_2COOH$[a]	$PhCH_2CONHTol$-*p*	84
p-$O_2NC_6H_4NH_2$	$PhCH_2COOH$[a]	$PhCH_2CONHC_6H_4NO_2$-*p*	58[d]
2-$NaphNH_2$	$PhCH_2COOH$[a]	2-NaphNHCOCH_2Ph	86
$PhNH_2$	PhCOOH[b]	PhCONHPh	61
p-$TolNH_2$	PhCOOH[b]	PhCONHTol-*p*	63
p-$O_2NC_6H_4NH_2$	PhCOOH[b]	$PhCONHC_6H_4NO_2$-*p*	40[d]
2-$NaphNH_2$	PhCOOH[b]	2-NaphNHCOPh	52[d]
c-$HexNH_2$	PhCOOH[b]	PhCONHHex-*c*	55
$PhNH_2$	*p*-ClC_6H_4COOH[b]	*p*-$ClC_6H_4CONHPh$	46
p-$TolNH_2$	*p*-ClC_6H_4COOH[b]	*p*-$ClC_6H_4CONHTol$-*p*	58
2-$NaphNH_2$	*p*-ClC_6H_4COOH[b]	$2\text{-NaphNHCOC}_6H_4Cl$-*p*	52[d]
p-$TolNH_2$	*p*-TolCOOH[b]	*p*-TolCONHTol-*p*	68
$PhNH_2$	*p*-TolCOOH[b]	*p*-TolCONHPh	64

[a]Four hours at 50–60 °C.
[b]One hour at 50–60 °C and four hours at 115–120 °C.
[c]Yields are of isolated crude products.
[d]Purified product.

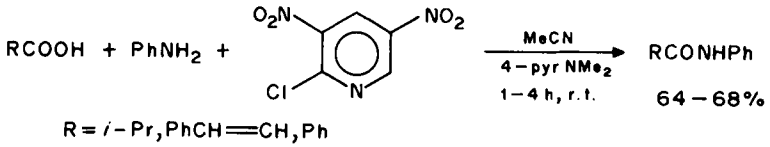
Reaction of carboxylic acids with aniline and triethylamine in the presence of polynitrohalobenzenes produces[2270] carboxanilides via the intermediate anion shown in equation 1219.



(1219)

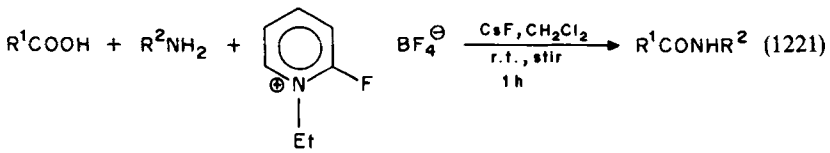
Polynitrohalobenzene	RCOOH	Conditions	Time (h)	Product	Yield (%)
$2,6\text{-}(NO_2)_2C_6H_3Cl$	$PhCH_2COOH$	Reflux, 2 h	0.5	$2,6\text{-}(NO_2)_2C_6H_3NHPh$	7
$2,6\text{-}(NO_2)_2C_6H_3F$	$PhCH_2COOH$	Reflux, 2 h	0.5	$PhCH_2CONHPh$ +	58
				$2,6\text{-}(NO_2)_2C_6H_3NHPh$	9
$2,4\text{-}(NO_2)_2C_6H_3Cl$	$PhCH_2COOH$	Reflux, 2 h	0.5	$PhCH_2CONHPh$ +	12
				$2,4\text{-}(NO_2)_2C_6H_3NHPh$	58
$2,4\text{-}(NO_2)_2C_6H_3F$	$PhCH_2COOH$	Reflux, 2 h	0.5	$PhCH_2CONHPh$ +	75
				$2,4\text{-}(NO_2)_2C_6H_3NHPh$	12
$2,4,6\text{-}(NO_2)_3C_6H_2Cl$	$PhCH_2COOH$	r.t., 3 h	0.5	$PhCH_2CONHPh$ +	48
				$2,4,6\text{-}(NO_2)_3C_6H_2NHPh$	52
$2,4,6\text{-}(NO_2)_3C_6H_2Cl$	$PhCH_2COOH$	Reflux, 2 h	0.5	$PhCH_2CONHPh$ +	44
				$2,4,6\text{-}(NO_2)_3C_6H_2NHPh$	40
$2,4,6\text{-}(NO_2)_3C_6H_2F$	$PhCH_2COOH$	Reflux, 2 h	0.5	$PhCH_2CONHPh$ +	89
				$2,4,6\text{-}(NO_2)_3C_6H_2NHPh$	4
$2,4,6\text{-}(NO_2)_3C_6H_2F$	$MeCOOH$	r.t., 1 h, N_2	1.5	$MeCONHPh$	82
$2,4,6\text{-}(NO_2)_3C_6H_2F$	$Me_2CHCOOH$	r.t., 1 h, N_2	2.5	$Me_2CHCONHPh$	96
$2,4,6\text{-}(NO_2)_3C_6H_2F$	Me_3CCOOH	r.t., 1 h, N_2	2.0	$Me_3CCONHPh$	93
$2,4,6\text{-}(NO_2)_3C_6H_2F$	$PhCH{=}CHCOOH$	r.t., 1 h, N_2	1.0	$PhCH{=}CHCONHPh$	100
$2,4,6\text{-}(NO_2)_3C_6H_2F$	$PhCOOH$	r.t., 1 h, N_2	1.0	$PhCONHPh$	93
$2,4,6\text{-}(NO_2)_3C_6H_2F$	$PhCH_2OCONHCH_2COOH$	r.t., 1 h, N_2	1.0	$PhCH_2OCONHCH_2CONHPh$	87

Similar results have been obtained[2271] using 2-chloro-3,5-dinitropyridine as the condensing agent for carboxylic acids and aniline in the presence of *p*-dimethylaminopyridine (equation 1220).



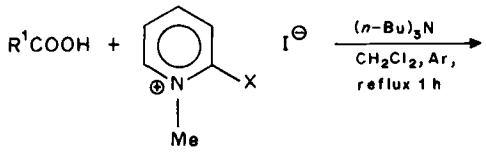
(1220)

Pyridinium salts in the presence of cesium fluoride[2272] or acid capture reagents such as tri-(*n*-butyl) amine[2273] or pyrimidinones[2274] have been reported to be very effective as coupling reagents for the preparation of amides from carboxylic acids and amines. Thus, reaction of a suspension containing cesium fluoride, 1-ethyl-2-fluoropyridinium tetrafluoroborate and a carboxylic acid in methylene chloride with an amine, also suspended in methylene chloride, produces[2272] the corresponding amide (equation 1221).



Acid	Amine	Product	Yield (%)
$Ph(CH_2)_3COOH$	$PhCH(Me)NH_2$	$Ph(CH_2)_3CONHCH(Me)Ph$	94
$PhCH_2OOCNHCH(CH_2Ph)COOH$	$EtOOCCH_2NH_2$	$PhCH_2OOCNHCH(CH_2Ph)CONHCH_2COOEt$	60

Similarly, reaction[2273] of carboxylic acids, amines and 1-methyl-2-halopyridinium iodide in the presence of tri-(*n*-butyl) amine affords the corresponding amides via the intermediate pyridinium ester salt shown in equation 1222.



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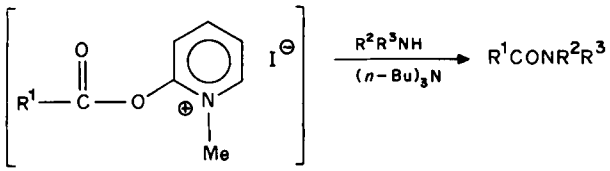
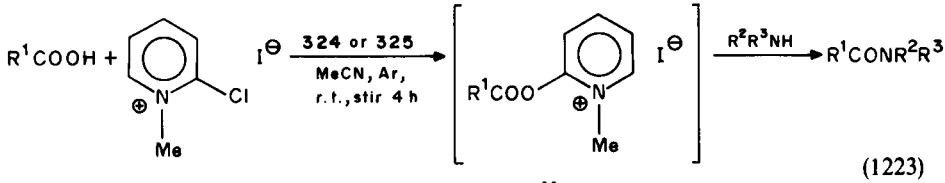


Acid	Halide in pyridinium salt X	Amine R^2	Amine R^3	Yield (%)
EtCOOH	Cl	$PhCH_2$	H	~100
EtCOOH	Cl	$PhCH_2$	Me	86
EtCOOH	Cl	Ph	H	82
t-BuCOOH	Cl	$PhCH_2$	H	93
$PhCH_2$	Cl	*n*-Bu	H	90
$PhCH_2$	Cl	*n*-Bu	*n*-Bu	95
$PhCH_2$	Cl	*t*-Bu	H	~100
$PhCH_2$	Cl	PhCH(Me)	H	93
$PhCH_2$	Br	*n*-C_8H_{17}	H	98
$PhCH_2CH_2$	Cl	*n*-Bu	H	88
$PhCH_2CH_2$	Cl	*n*-Bu	*n*-Bu	98
$PhCH_2CH_2$	Cl	$PhCH_2$	H	96
$PhCH_2CH_2$	Cl	Ph	H	91
$PhCH_2$	Br	$PhCH_2$	H	~100
$PhCH_2$	Br	Ph	H	~100
Ph	Cl	*n*-Bu	*n*-Bu	~100
Ph	Cl	$PhCH_2$	H	95
Ph	Br	Ph	H	85

Using 1-methyl-2-chloropyridinium iodide as the coupling reagent, and either 3,4-dihydro-9-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (**324**) or 3,4-dihydro-3,9-dimethyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (**325**) as the acid capture reagent, also produced[2274] excellent yield of amides from carboxylic acids and amines via the same pyridinium ester salt intermediate (equation 1223).



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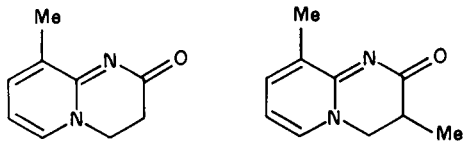


(**324**) (**325**)

Acid	Amine R^2	Amine R^3	% Yield using **324**	% Yield using **325**
EtCOOH	$PhCH_2$	Me	80	
$PhCH_2COOH$	*n*-Bu	H	98	~100
$PhCH_2COOH$	*n*-C_8H_{17}	H	92	

(*continued*)

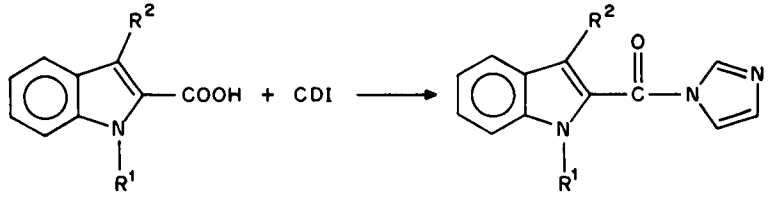
Acid	Amine R^2	Amine R^3	% Yield using 324	% Yield using 325
$PhCH_2COOH$	*i*-Pr	*i*-Pr	87	
$PhCH_2COOH$	*t*-Bu	H	89	89
$PhCH_2COOH$	Ph	H	99	99
$PhCH_2COOH$	Ph	Me	88	
$PhCH_2CH_2COOH$	*t*-Bu	H	90	
$PhCH_2CH_2COOH$	$PhCH_2$	Me	93[a]	84
$PhCH_2CH_2COOH$	Ph	H	~100	~100
$PhCH_2CH_2COOH$	Ph	Me	90	
Ph	*n*-Bu	H	~100	
Ph	*t*-Bu	H	96[a]	
Ph	$PhCH_2$	Me	82	
Ph	Ph	H	79[a]	82
Ph	Ph	Me	82	

[a]Reaction was refluxed for 2 hours.

N,N'-Carbonyldiimidazole (CDI) has been used[2275] as a condensing agent to produce *N*-acyl aziridines from carboxylic acids and benzylaziridine (equation 1224), and as both a condensing agent and a reagent in the production[2276] (equation 1225) of indole-2-carboxamides from 2-carboxyindoles.

R = H, Me, Et, *i*-Pr, *t*-Bu, *c*-Hex, Ph, 3-Pyr, *E*-C_3H_5, *E,E*-C_5H_7

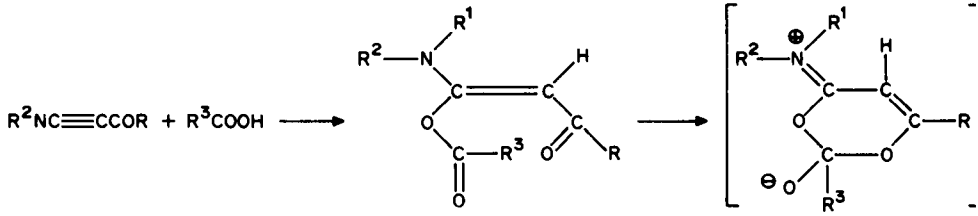
(1224)



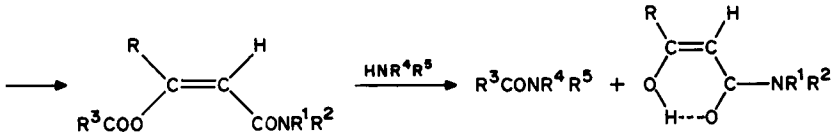
R^1 = H, Me; R^2 = H, CHO

(1225)

An interesting one-pot preparation of amides involves the use of nitrogen-containing 'push–pull' acetylenes as condensing agents[2277] for carboxylic acids and amines. The reaction proceeds by initial formation of an enol ester, which then reacts with an amine to produce the corresponding amide (equation 1226).



(1226)



R^3	R^4	R^5	Amide	Yield (%)
Me	Et	Et	$MeCONEt_2$	94
Me	H	*i*-Pr	MeCONHPr-*i*	95
Et	Et	Et	$EtCONEt_2$	89
Et	H	*i*-Pr	EtCONHPr-*i*	92
CH_2=CH	Et	Et	CH_2=$CHCONEt_2$	87
CH_2=CH	H	*i*-Pr	CH_2=CHCONHPr-*i*	88
(*E*)-MeCH=CH	Et	Et	(*E*)-MeCH=$CHCONEt_2$	95
(*E*)-MeCH=CH	H	*i*-Pr	(*E*)-MeCH=CHCONHPr-*i*	89
HC≡C	H	*i*-Pr	HC≡CCONHPr-*i*	89
$Et_2NCOCH_2CH_2$	Et	Et	$Et_2NCOCH_2CH_2CONEt_2$	73

Recently, phosphorous-containing reagents, either alone or in combination with other molecules, have been extensively used as condensing agents in the preparation of amides from carboxylic acids and amines.

Treatment of carboxylic acids with *o*-nitrophenyl thiocyanate and tri-*n*-butylphosphine in tetrahydrofuran containing an amine has been reported[2278] to result in the direct high-yield conversion of acids into amides via the mechanism shown in equation 1227.

$$o\text{-}O_2NC_6H_4SCN + (n\text{-Bu})_3P \xrightarrow{THF} o\text{-}O_2NC_6H_4S\overset{\oplus}{P}(Bu\text{-}n)_3CN^{\ominus}$$

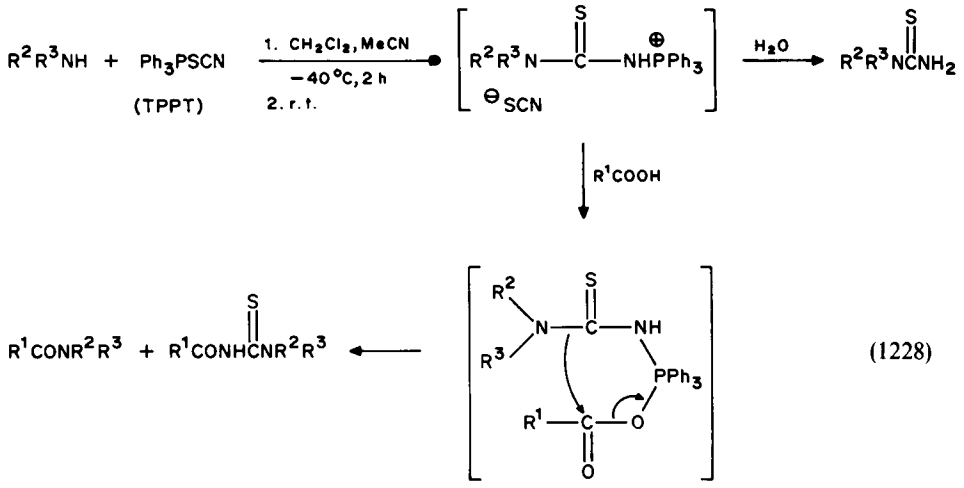
$$\xrightarrow{R^1COOH} R^1COO\overset{+}{P}(Bu\text{-}n)_3 + o\text{-}O_2NC_6H_4S^- + HCN \qquad (1227)$$

$$\xrightarrow{HNR^2R^3} R^1CONR^2R^3 + (n\text{-Bu})_3PO$$

R^1	R^2	R^3	Time (h)	Amide	Yield (%)
c-Hex	$CH_2{=}CHCH_2$	H	7	*c*-HexCONHCH$_2$CH=CH$_2$	100
c-Hex	*i*-Bu	H	8	*c*-HexCONHBu-*i*	99
c-Hex	Et	Et	8	*c*-HexCONEt$_2$	96
c-Hex	$PhCH_2$	H	6.5	*c*-HexCONHCH$_2$Ph	99
n-C_7H_{15}	$CH_2{=}CHCH_2$	H	7	*n*-C_7H_{15}CONHCH$_2$CH=CH$_2$	98
n-C_7H_{15}	*i*-Bu	H	8	*n*-C_7H_{15}CONHBu-*i*	96
n-C_7H_{15}	Et	Et	6	*n*-C_7H_{15}CONEt$_2$	94
n-C_7H_{15}	$PhCH_2$	H	7	*n*-C_7H_{15}CONHCH$_2$Ph	99
n-C_7H_{15}	1-Pip		7	*n*-C_7H_{15}COPip-1	99
Ph	$CH_2{=}CHCH_2$	H	5.5	PhCONHCH$_2$CH=CH$_2$	100
Ph	*i*-Bu	H	6.5	PhCONHBu-*i*	96
Ph	Et	Et	5.5	PhCONEt$_2$	100
Ph	$PhCH_2$	H	6.5	PhCONHCH$_2$Ph	96
p-ClC_6H_4	$CH_2{=}CHCH_2$	H	4.5	*p*-ClC_6H_4CONHCH$_2$CH=CH$_2$	92
p-ClC_6H_4	*i*-Bu	H	4	*p*-ClC_6H_4CONHCONHBu-*i*	93
p-ClC_6H_4	Et	Et	4.5	*p*-ClC_6H_4CONNEt$_2$	94
p-ClC_6H_4	$PhCH_2$	H	5.5	*p*-ClC_6H_4CONHCH$_2$Ph	100
p-An	$PhCH_2$	H	12	*p*-AnCONHCH$_2$Ph	98
$Me_2C{=}CH$	$PhCH_2$	H	—	$Me_2C{=}CHCONHCH_2Ph$	96
$H_2C{=}CH$	$PhCH_2$	H	—	$H_2C{=}CHCONHCH_2Ph$ + *o*-$O_2NC_6H_4SCH_2CONHCH_2Ph$	17 61

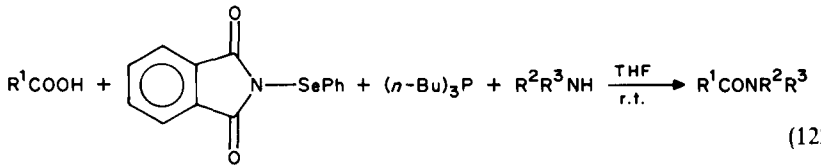
A similar approach using the combined reagent triphenylphosphine–thiocyanogen (TPPT) has also been reported[2279]. Thus, reaction of TPPT in methylene chloride with an amine in acetonitrile produces a thiocarbamoylaminophosphonium salt which, upon hydrolysis, produces 1,1-disubstituted thioureas (equation 1228). However, if the intermediate is treated with a carboxylic acid instead of water, an amide and/or an acylthiourea are produced (equation 1228).

Treatment of carboxylic acids with *N*-phenylselenophthalimide and tri-*n*-butylphosphine in the presence of an amine produces[2280] amides in yields ranging from 82 to 98 percent (equation 1229).



(1228)

R^1	R^2	R^3	Product	Yield (%)
—	Me	$PhCH_2$	$PhCH_2(Me)NCSNH_2$	65
—	Me	Ph	$PhMeNCSNH_2$	80
—	Et	Ph	$PhEtNCSNH_2$	50
—		$—(CH_2)_5—$	1-$PipCSNH_2$	70
—		$—(CH_2)_4—$	1-$PyrrolidinylCSNH_2$	77
—	Et	Et	Et_2NCSNH_2	70
—	Me	*c*-Hex	*c*-$Hex(Me)NCSNH_2$	70
$PhCH_2$	Me	$PhCH_2$	$MeCON(Me)CH_2Ph$ +	19
			$MeCONHCSN(Me)CH_2Ph$	28
c-Hex	Me	$PhCH_2$	*c*-$HexCONHCSN(Me)CH_2Ph$	31
Me	H	Ph	MeCONHMe	72
n-Pen	H	Ph	*n*-PenCONHPh +	45
			n-PenCONHCSNHPh	13
$PhCH_2$	H	Ph	$PhCH_2CONHPh$ +	62
			$PhCH_2CONHCSNHPh$	21
c-Hex	H	Ph	*c*-HexCONHPh +	16
			c-HexCONHCSNHPh	45
Ph	H	Ph	PhCONHCSNHPh	42
$PhCH_2$	Me	Ph	$PhCH_2CONMePh$ +	8
			PhCONHCSNMePh	89
$PhCH_2$	Et	Ph	$PhCH_2CONHCSNEtPh$	83
$PhCH_2$	*s*-Bu	Ph	$PhCH_2CONHCSN(s\text{-}Bu)Ph$	75



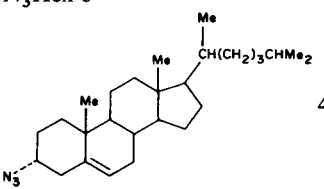
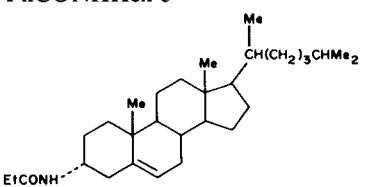
(1229)

R^1	R^2	R^3	Time (h)	Product	Yield (%)
$PhCH_2$	H	*i*-Pr	3.0	$PhCH_2CONHPr\text{-}i$	95
$PhCH_2$	Et	Et	2.3	$PhCH_2CONEt_2$	98
$PhCH_2$	H	$PhCH_2$	2.0	$PhCH_2CONHCH_2Ph$	93
p-An	H	*i*-Pr	3.0	*p*-$AnCONHPr\text{-}i$	95
p-An	Et	Et	2.5	*p*-$AnCONEt_2$	88
p-ClC_6H_4	H	*i*-Pr	3.5	*p*-$ClC_6H_4CONHPr\text{-}i$	95
p-ClC_6H_4	Et	Et	2.5	*p*-$ClC_6H_4CONEt_2$	92
n-C_7H_{15}[a]	H	*i*-Pr	2.5	*n*-$C_7H_{15}CONHPr\text{-}i$	98
c-Hex	H	*i*-Pr	3.0	*c*-$HexCONHPr\text{-}i$	90
c-Hex	Et	Et	1.8	*c*-$HexCONEt_2$	82
c-HexCHMe	H	*i*-Pr	2.0	*c*-$HexCHMeNHPr\text{-}i$	93

[a]Reaction was run at 0 °C.

$$Ph_3P + R^2N_3 \xrightarrow[N_2,\ several\ h]{anhyd\ C_6H_6,\ heat} [Ph_3P{=}NR^2] \xrightarrow{R^1COOH} R^1COO^{\ominus}$$

$$+ Ph_3\overset{\oplus}{P}NHR^2 \rightleftharpoons \left[\ Ph_3P\ \ O{-}C(=O){-}R^1\ \ NHR^2\ \right] \longrightarrow Ph_3PO + R^1CONHR^2 \qquad (1230)$$

Acid	Azide	Time (h)	Product	Yield (%)
EtCOOH	$N_3CH_2CH_2CHMe_2$	24	$EtCONHCH_2CHMe_2$	88
EtCOOH	N_3CH_2Ph	24	$EtCONHCH_2Ph$	95
EtCOOH	N_3Ph	60	EtCONHPh	96
EtCOOH	N_3Hex-*c*	12	EtCONHHex-*c*	95
PhCOOH	$N_3CH_2CH_2CHMe_2$	48	$PhCONHCH_2CH_2CHMe_2$	75
PhCOOH	N_3CH_2Ph	48	$PhCONHCH_2Ph$	78
PhCOOH	N_3Ph	5[a]	PhCONHPh	96
PhCOOH	N_3Hex-*c*	12	PhCONHHex-*c*	85
EtCOOH		42		81
$PhCONHCH_2COOH$	$N_3CH_2CH_2CHMe_2$	4[a]	$PhCONHCH_2CONHCH_2CH_2CHMe_2$	60
$MeCON(Me)CH_2COOH$	N_3CH_2Ph	32[b]	$MeCON(Me)CH_2CONHCH_2Ph$	77
$ClCH_2COOH$	$N_3(CH_2)_3COOMe$	2[a]	$ClCH_2CONH(CH_2)_3COOMe$	65
Z-Ile-Val OH	N_3CH_2Ph	32[b]	Z-Ile-Val-$NHCH_2Ph$	56
$MeCO_2Bu$-*n*	N_3R[c]	—	No reaction	—
$MeCO_2Et$	N_3R[c]	—	No reaction	—

[a] Days.
[b] Toluene used as solvent.
[c] R unspecified.

An interesting preparation of amides reported[2281] in the recent literature utilizes an application of the Staudinger reaction and involves the triphenylphosphine-mediated formation of amides from carboxylic acids and azides according to the mechanism shown in equation 1230.

Amide and polyamide preparation has also been accomplished[2282] by reaction of carboxylic acids and amines in the presence of triphenyl phosphite and quaternary ammonium or pyridinium salts (equation 1231). This approach was extended to the polycondensation of amino acids in the presence of polyvinylpyrrolidone as a matrix to give poly(β-alanine) with high molecular weights.

$$R^1COOH + R^2NH_2 \xrightarrow[\text{base}]{P(OPh)_3} R^1CONHR^2$$

$$R^3(COOH)_2 + R^4(NH_2)_2 \xrightarrow[\text{base}]{P(OPh)_3} R^3(CONH)_2R^4 \qquad (1231)$$

Example of the use of phosphorous halides, sulfides and oxides as condensing agents for carboxylic acids and amines for the production of amides are all represented in the recent literature. Examples of the use of phosphorous halides include the preparation of carboxamides in 67 to 91 percent yields by reaction[2283] of amines with triacyl phosphites, generated *in situ* from a carboxylic acid and phosphorous trichloride in pyridine (equation 1232), the preparation of amides catalyzed by complexes of phosphorous acid and iodine in pyridine[2284] (equation 1233), and the use of diphosphorous tetraiodide as a condensing agent for the preparation[2285] of amides and peptides (equation 1234).

$$R^1COOH + PCl_3 \xrightarrow{C_5H_5N} (R^1COO)_3P \xrightarrow{R^2NH_2} R^1CONHR^2 \quad 67\text{–}91\% \qquad (1232)$$

$$R^1COOH + R^2R^3NH \xrightarrow[75\text{–}85\,^\circ C,\ 5\text{–}6\,h]{H_3PO_3 + I_2\ \text{complex}} R^1CONR^2R^3 \qquad (1233)$$

$$R^1COOH + R^2NH_2 \xrightarrow[2,6\text{-lutidine, reflux}]{P_2I_4,\ CCl_4\text{–}CH_2Cl_2} R^1CONHR^2 \qquad (1234)$$

R^1	R^2	Product	Yield (%)
p-An	Ph	*p*-AnCONHPh	~100
p-An	$PhCH_2$	*p*-AnCONHCH$_2$Ph	90
3,4-$(MeO)_2C_6H_3$	Ph	3,4-$(MeO)_2C_6H_3$CONHPh	~100
3,4-$(MeO)_2C_6H_3$	$PhCH_2$	3,4-$(MeO)_2C_6H_3$CONHCH$_2$Ph	98
p-Tol	Ph	*p*-TolCONHPh	80
p-Tol	2,4,6-$(MeO)_3C_6H_2$	*p*-TolCONHC$_6$H$_2$(OMe)$_3$-2,4,6	~100
2,4,6-$Me_3C_6H_2$	Ph	2,4,6-$Me_3C_6H_2$CONHPh	~100
4-Cl-2,3,5,6-Me_4C_6	Ph	4-Cl-2,3,5,6-Me_4C_6CONHPh	~100
p-$MeCOC_6H_4$	Ph	*p*-$MeCOC_6H_4$CONHPh	81
p-$O_2NC_6H_4$	Ph	*p*-$O_2NC_6H_4$CONHPh	~100
p-$O_2NC_6H_4$	$PhCH_2$	*p*-$O_2NC_6H_4$CONHCH$_2$Ph	80
PhCH=CH_2	Ph	PhCH=CH$_2$CONHPh	~100

R^1	R^2	Product	Yield (%)
t-Bu	Ph	*t*-BuCONHPh	~100
t-Bu	$PhCH_2$	*t*-$BuCONHCH_2Ph$	~100
t-Bu	2,6-$Me_2C_6H_3$	*t*-$BuCONHC_6H_3Me_2$-2,6	~100
t-Bu	3,5-$Me_2C_6H_3$	*t*-$BuCONHC_6H_3Me_2$-3,5	~100
t-Bu	*p*-$O_2NC_6H_4$	*t*-$BuCONHC_6H_4NO_2$-*p*	85
$PhCH_2CH(NHCOMe)$	$EtOOCCH_2$	$PhCH_2CHCONHCH_2COOEt$ | $NHCOMe$	46
$PhCH_2CH$- | $NHCO_2CH_2Ph$	$EtOOCH_2$	$PhCH_2CHCONHCH_2COOEt$ | $NHCO_2CH_2Ph$	53

At least one recent report[2286] describes the use of diphosphorous pentasulfide as a condensation and thionation reagent for carboxylic acids and amines during the production of thioamides (equation 1235).

$$3,4,5\text{-}(MeO)_3C_6H_2COOH + \text{Morpholine} \xrightarrow[\text{reflux, 2.5 h}]{P_2S_5,\ C_5H_5N} 3,4,5\text{-}(MeO)_3C_6H_2C(=S)\text{Morpholino} \quad (1235)$$

Similarly, another report[2287] describes the use of phosphorous pentoxide in the preparation of antidepressant *N,N'*-dialkylamidines from the corresponding carboxylic acids and amine hydrochlorides (equation 1236).

$$R^1COOH + R^2NH_2\cdot HCL \xrightarrow[c\text{-HexNMe}_2]{P_2O_5} R^1\text{—}\overset{\overset{NR^2}{\|}}{C}\text{—}NHR^2 \quad (1236)$$

30–83%

R^1 = Ph, ClC_6H_4, $Cl_2C_6H_3$, *p*-Tol, $PhCH_2$, Ph_2CH, Me_2CH
R^2 = Me, *n*-Pr, CH_2CHMe_2.

Another phosphorous-containing reagent[2288] which has been used as a condensation reagent for carboxylic acids and amines is phenyl *N*-phenylphosphoramidoazidate, which produces disubstituted ureas (equation 1237).

$$R^1COOH + R^2NH_2 + \underset{\underset{N_3}{|}}{PhOPNHPh} \xrightarrow[\text{reflux}]{MeCN} R^1NHCONHR^2 \quad (1237)$$

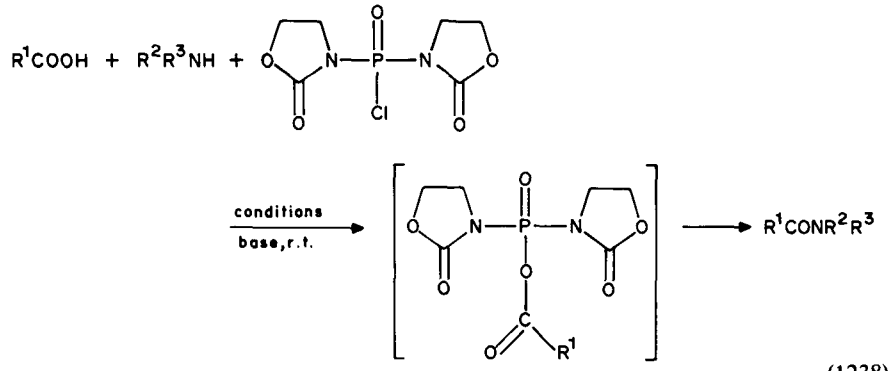
60–94%

R^1 = Ph, $PhCH_2$, *p*-ClC_6H_4
R^2 = Ph, $PhCH_2$, 2-pyridyl

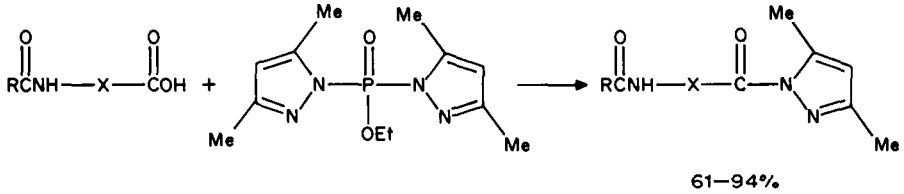
Reaction of carboxylic acids or their amine salts with mono- or dialkylamines in the presence of *N,N*-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride pro-

duces[2289,2290] amides according to the mechanism shown in equation 1238. The structural variety of substrates used and amide products formed are reported in Table 112.

A similar reagent which has been used to prepare[2291] *N*-acyl amino acid pyrazolides from *N*-acyl amino acids is ethyl *N,N*-bis(3,5-dimethylpyrazolyl)phosphorodiamidoate. When used to produce amides this compound acts as both a reactive substrate and a condensing agent (equation 1239). Similar results[2291] are obtained with the unsubstituted phosphorodiamidoate (equation 1240), with the sulfoxide analogue of the diamidoate

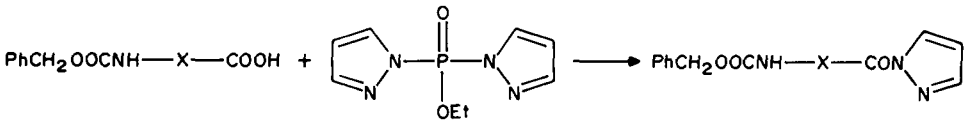


(1238)



R = $PhCH_2O$, *p*-$MeC_6H_4SO_2O$, *N*-Phthalimido CH_2O
X = CH_2, CHMe(DL), CHPh(DL), CMe_2, $CHCH_2SMe$(DL), MeC(OH)(DL), $CHCH_2COOH$

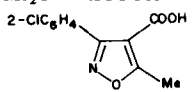
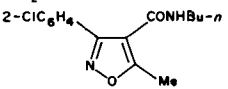
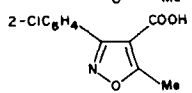
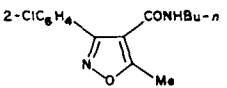
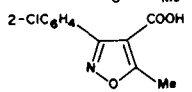
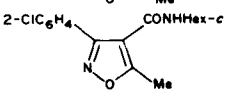
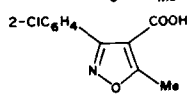
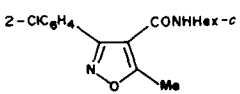
(1239)

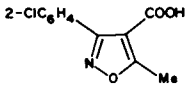
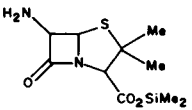
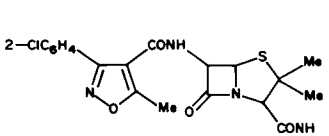
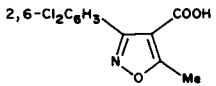
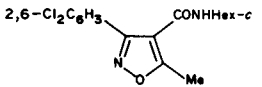
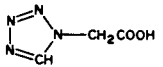
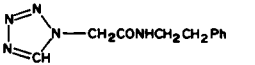
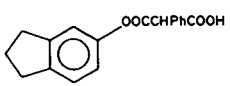
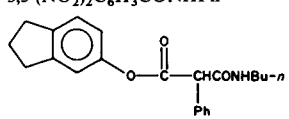
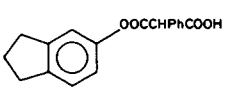
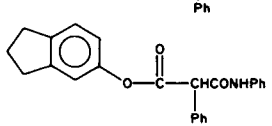
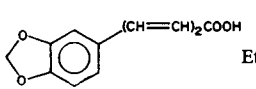
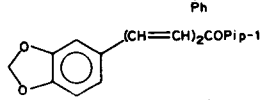


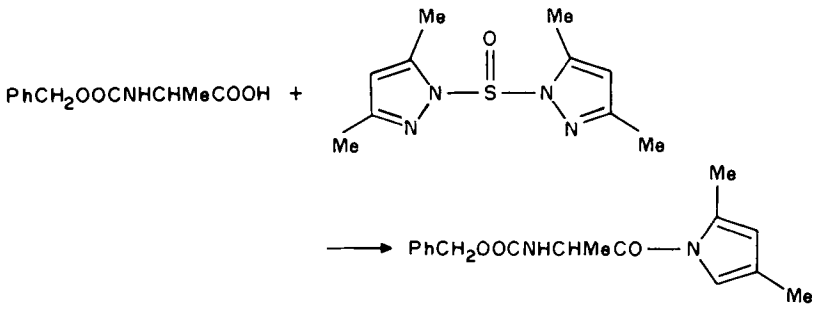
X = CH_2, CHPh (DL)

(1240)

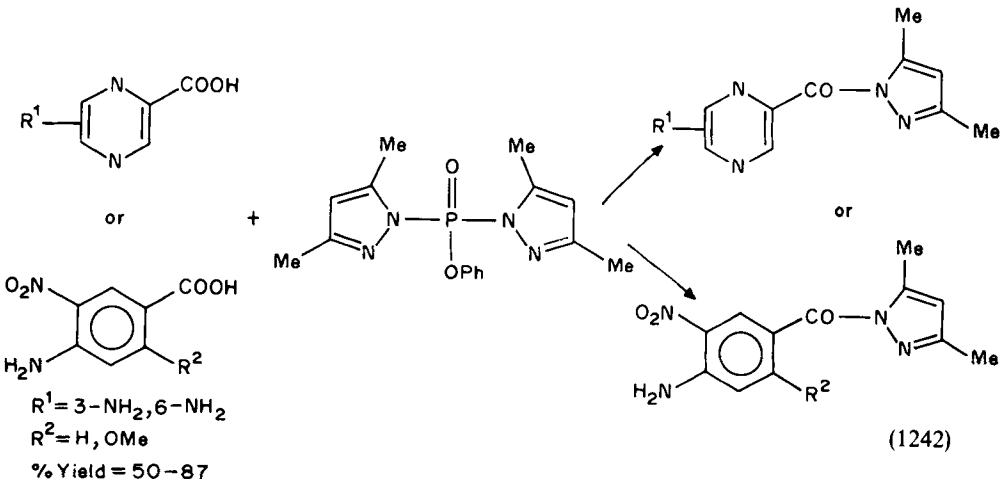
TABLE 112. Preparation of amides using *N,N*-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride

Acid	Amine base	Solvent	Time (min)	Amine Reactant	Product	Yield (%)	Reference
t-BuCOOH	Et_3N	CH_2Cl_2	120	*c*-$HexNH_2$	*t*-BuCONHHex-*c*	84	2289
t-BuCOOH	Et_3N	CH_2Cl_2	75	(*D*)-(+)PhCH(Me)NH_2	*t*-BuCONHCH(Me)Ph	91	2289
PhCH(Br)COOH	Et_3N	CH_2Cl_2	60	*c*-$HexNH_2$	PhCH(Br)CONHHex-*c*	82	2289
(*D,L*)PhCH(N_3)COOH	Et_3N	CH_2Cl_2	120	*c*-$HexNH_2$	PhCH(N_3)CONHHex-*c*	95	2289
(*L*)-(+)PhCHCOOH N_3	Et_3N	$MeCONMe_2$	90	*p*-$O_2NC_6H_4$CH(OH)CH(NH_2)CH_2OH	PhCHCONHCH(OH)CH$C_6H_4NO_2$-*p* N_3 CH_2OH	83	2289
(*D*)-(−)PhCHCOOH N_3	N-Et Morpholine	$MeCONMe_2$	90	*p*-$O_2NC_6H_4$CH(OH)CH(NH_2)CH_2OH	PhCHCONHCH(OH)CH$C_6H_4NO_2$-*p* N_3 CH_2OH	84	2289
PhOOCCHCOOH Ph	C_5H_5N	MeCN	20	*o*-$TolNH_2$	PhOOCCHCONHTol-*o* Ph	70	2290
$H_2C{=}CMeCOOH$	N-Et Morpholine	CH_2Cl_2	120	$PhCH_2CH_2NH_2$	$H_2C{=}CMeCONHCH_2CH_2Ph$	85	2289
$MeCH{=}CHCOOH$	Et_3N	CH_2Cl_2	60	Piperidine	$MeCH{=}CHCOPip\text{-}1$	100	2289
$Me_2C{=}CHCOOH$	N-Et Morpholine	CH_2Cl_2	120	Morpholine	$Me_2C{=}CHCO(4\text{-}Morpholino)$	94	2289
$Me_2C{=}CHCOOH$	N-Et Morpholine	CH_2Cl_2	120	Piperidine	$Me_2C{=}CHCOPip\text{-}1$	92	2289
$Me_2C{=}CHCOOH$	N-Et Morpholine	$MeCONMe_2$	75	(*D*)-(+)PhCH(*Me*)NH_2	$Me_2C{=}CHCONHCHMePh$	45	2289
$Me_2C{=}CHCOOH$	Et_3N	$MeCONMe_2$	75	(*D*)-(+)PhCH(Me)NH_2	$Me_2C{=}CHCONHCHMePh$	77	2289
$Me_2C{=}CHCOOH$	DBU	$MeCONMe_2$	75	(*L*)-(−)PhCH(Me)NH_2	$Me_2C{=}CHCONHCHMePh$	74	2289
$Me_2C{=}CHCOOH$	Et_2N	$MeCONMe_2$	75	(*L*)-(−)PhCH(Me)NH_2	$Me_2C{=}CHCONHCHMePh$	76	2289
	N-Et Morpholine	CH_2Cl_2	60	*n*-$BuNH_2$		94	2289
	Et_3N	CH_2Cl_2	60	*n*-$BuNH_2$		99	2289
	N-EtMorpholine	CH_2Cl_2	70	*c*-$HexNH_2$		84	2289
	Et_3N	$MeCONMe_2$	75	*c*-$HexNH_2$		94	2289

	Et_3N	CH_2Cl_2	100			89	2290
	Et_3N	$MeCONMe_2$	60	c-$HexNH_2$		98	2289
	*N*-Et Morpholine	CH_2Cl_2	60	$PhCH_2CH_2NH_2$		94	2289
p-ClC_6H_4COOH	Et_3N	CH_2Cl_2	90	Piperidine	p-ClC_6H_4COPip-1	91	2289
2,6-$Cl_2C_6H_3COOH$	N-Et Morpholine	CH_2Cl_2	45	2,6-$Me_2C_6H_3NH_2$	2,6-$Cl_2C_6H_3CONHC_6H_3Me_2$-2,6	90	2290
2,6-$(MeO)_2C_6H_3COOH$	Et_3N	CH_2Cl_2/ n-C_6H_{14}	30	n-$BuNH_2$	2,6-$(MeO)_2C_6H_3CONHBu$-n	93	2290
2,6-$(MeO)_2C_6H_3COOH$	Et_3N	CH_2Cl_2/ n-C_6H_{14}	20	$PhNH_2$	2,6-$(MeO)_2C_6H_3CONHPh$	91	2290
3,4,5-$(MeO)_3C_6H_2COOH$	Et_3N	CH_2Cl_2/ n-C_6H_{14}	30	$PhNH_2$	3,4,5-$(MeO)_3C_6H_2CONHPh$	95	2290
2,6-$(O_2N)_2C_6H_3COOH$	Et_3N	CH_2Cl_2	45	$PhNH_2$	2,6-$(NO_2)_2C_6H_3CONHPh$	100	2290
3,5-$(NO_2)_2C_6H_3COOH$	Et_3N	CH_2Cl_2	—	$PhNH_2$	3,5-$(NO_2)_2C_6H_3CONHPh$	95	2290
	C_5H_5N	MeCN	30	n-$BuNH_2$		26	2290
	C_5H_5N	MeCN	30	$PhNH_2$		73	2290
 (*trans, trans*)	Et_3N	CH_2Cl_2	60	Piperidine	 (*trans, trans*)	90	2289



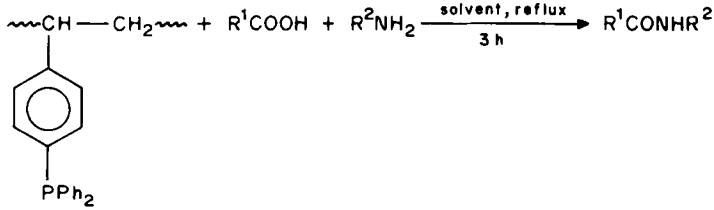
(1241)



(1242)

(equation 1241) and with the phenyl ester of *N,N*-bis(3,5-dimethylpyrazolyl)-phosphorodiamine (equation 1242).

An interesting preparation of amides from carboxylic acids and amines utilizes[2243,2292] a 1 percent cross-linked polymer containing 2.5 millimoles of phosphine per gram of

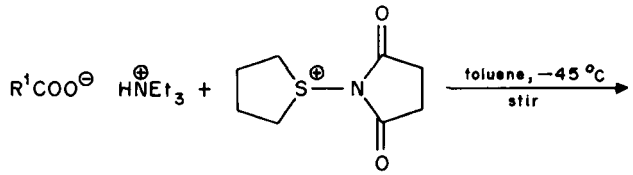


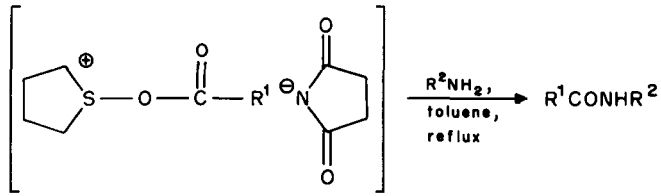
(1243)

R^1	R^2	Solvent	Yield (%)
n-$C_{17}H_{35}$	Ph	$ClCH_2CH_2Cl$, CCl_4	86
$PhOCH_2$	Ph	CCl_4	57
$PhOCH_2$	Ph	$ClCH_2CH_2Cl$, CCl_4	72
(*trans*) PhCH=CH	*p*-Tol	CCl_4	83
Ph	*p*-Tol	CCl_4	94
p-PhC_6H_4	Ph	$ClCH_2CH_2Cl$, CCl_4	73

polymer as the condensing agent (equation 1243). At the end of the reaction all the phosphorous-containing byproducts are removed by filtration of the polymer.

Treatment of the triethylammonium salts of carboxylic acids with a primary amine in the presence of *N*-tetrahydrothienylsuccinimide affords[2293] monosubstituted amides in 5 to 78 percent yields according to the mechanism shown in equation 1244.





(1244)

R^1	R^2	Yield (%)
Me	$PhCH_2$	50
Et	$PhCH_2$	5
Et	Ph	6
t-Bu	Ph	9
Ph	$PhCH_2$	6
Ph	*n*-Bu	6
Ph	*t*-Bu	11
$PhCH_2$	$PhCH_2$	60
$PhCH_2$	*n*-Bu	40
$PhCH_2$	*t*-Bu	78

Several examples of tin reagents used as condensing agents for the formation of amides have been reported in the recent literature. Thus, reaction of tin tetrahalide coordinated nitriles with similarly coordinated carboxylic acids produces[2294] *N*-acyl amides along with unsubstituted amides and anhydrides. The tin coordinated amides are reported[2294] to retard the reaction, while the tin coordinated anhydrides are reported to accelerate the reaction. Much better yields of amides are obtained[2295], however, when mono- or dialkyl tin halides, hydroxides and/or carboxylates are used as condensing agents for the reaction of carboxylic acids and ammonia gas (equation 1245), or when 1,1-dimethylstannocene is employed[2296] as the condensing agent (equation 1246).

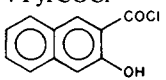
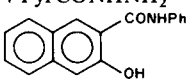
*2. *Acylation with acyl halides*

Acylation of amines with acid chloride still remains a viable method of preparation of amides. Using the general reaction shown in equation 1247, a variety of amides have been prepared (Table 113).

An interesting approach to the preparation of *N*-(1-methoxyalkyl) amides involves[2301]

TABLE 113. Preparation of amides from acid chlorides and amines

Acid chloride	Amine	Amide Product	Yield (%)	Reference
HCOCl	$PhNH_2$	HCONHPh	13	2297
MeCOCl	$PhNH_2$	MeCONHPh	84	2298
MeCOCl	p-$H_2NC_6H_4OH$	$MeCONHC_6H_4OH$-p + p-$MeCOOC_6H_4NHCOMe$	55 35	2298
n-$C_7H_{15}COCl$[a]	NH_3	n-$C_7H_{15}CONH_2$	63	2243
n-$C_{17}H_{35}COCl$[a]	NH_3	n-$C_{17}H_{35}CONH_2$	82	2242
n-$C_{17}H_{35}COCl$	$PhNH_2$	n-$C_{17}H_{35}CONHPh$	67	2297
CH_2=$CH(CH_2)_8COCl$	$PhNH_2$	CH_2=$CH(CH_2)_8CONHPh$	65	2297
$PhCH_2COCl$	$PhNH_2$	$PhCH_2CONHPh$	86	2298
$PhCH_2COCl$[a]	p-$TolNH_2$	$PhCH_2CONHTol$-p	50	2293
$Ph_2CHCOCl$	$PhNH_2$	$Ph_2CHCONHPh$	65	2297
$PhOCH_2COCl$[a]	$PhNH_2$	$PhOCH_2CONHPh$	50–60	2293
H_2NCH_2COCl	H_2NCH_2COOEt	$H_2NCH_2CONHCH_2COOEt$	40	2298
$Me_2CHCH(NH_2)COCl$	H_2NCH_2COOEt	$Me_2CHCH(NH_2)CONHCH_2COOEt$	45	2298
$Me_3COOCNHCH(CHMe_2)COCl$	H_2NCH_2COOEt	$Me_3COOCNHCH(CHMe_2)CONHCH_2COOEt$	38	2298
$O_2NN(Me)CH_2CH_2COCl$	NH_3	$O_2NN(Me)CH_2CH_2CONH_2$	91	2300
$O_2NN(Et)CH_2CH_2COCl$	NH_3	$O_2NN(Et)CH_2CH_2CONH_2$	84	2300
$O_2NN(Me)CH_2CH_2COCl$	$PhNH_2$	$O_2NN(Me)CH_2CH_2CONHPh$	85	2300
$O_2NN(Et)CH_2CH_2COCl$	$PhNH_2$	$O_2NN(Et)CH_2CH_2CONHPh$	84	2300
$O_2NN(Me)CH_2CH_2COCl$	Morpholine	$O_2NN(Me)CH_2CH_2CO$(-N- morpholino)	91	2300
CCl_3COCl	$PhNH_2$	$CCl_3CONHPh$	70	2297

CF_3COCl	H_2NCH_2COOH	$CH_3CONHCH_2COOH$	20	2297
CF_3COCl	Me_2NH	$CH_3CONHMe_2$	100	2297
CF_3COCl	$Me_2CHCH(NH_2)COOH$	$CF_3CONHCH(CHMe_2)COOH$	60	2297
CF_3COCl	$Me_2CHCH(NH_2)COOH$	$CF_3CONHCH(CHMe_2)COOH$	50	2298
CF_3COCl	$PhNH_2$	$CF_3CONHPh$	64	2298
PhCH=CHCOCl (*trans*)	$PhNH_2$	PhCH=CHCONHPh	93	2298
PhCH=CHCOCl[a] (*trans*)	*p*-$TolNH_2$	PhCH=CHCONHTol-*p*	77	2243
2-FuCOCl[a]	*p*-$TolNH_2$	2-FuCONHTol-*p*	82	2292
PhCOCl	$PhNH_2$	PhCONHPh	87	2298
PhCOCl[a]	*p*-$TolNH_2$	PhCONHTol-*p*	90	2293
PhCOCl	*o*-$(H_2N)_2C_6H_4$	*o*-$C_6H_4(NHCOPh)_2$	68	2298
PhCOCl	*o*-$H_2NC_6H_4OH$	*o*-$PhCOOC_6H_4NHCOPh$	73	2298
p-$O_2NC_6H_4COCl$	$PhNH_2$	*p*-$O_2NC_6H_4CONHPh$	71	2297
4-PyrCOCl	$PhNH_2$	4-PyrCONHPh	69	2297
4-PyrCOCl	$H_2NNH_2 \cdot H_2O$	4-PyrCONHNH_2	52	2297
	$PhNH_2$		61	2298
ClOC-COCl	$PhNH_2$	PhNHCO-CONHPh	52	2298
$(CH_2)_2(COCl)_2$	$PhNH_2$	$(CH_2)_2(CONHPh)_2$	45–55	2297, 2298
2,3-$(ClOC)_2C_6H_3NO_2$	$PhNH_2$	2,3-$(PhNHOC)_2C_6H_3NO_2$	64	2297

[a]Acid chloride formed as an intermediate in the reaction but not isolated.

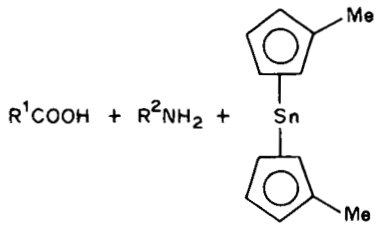
General:

$$R^1COOH + NH_3(g) \xrightarrow[R^2_2\,SnX_2]{R^2SnX_3\ or} R^1CONH_2 \qquad (1245)$$

R^1 = aliphatic, cycloaliphatic or aromatic C_6–C_{24}, esters, anhydrides
R^2 = C_1–C_{12} hydrocarbons
X = OH, halogen, C_2–C_6 carboxylates

Specific Example:

$$Me(CH_2)_7CH{=}CH(CH_2)_{11}COOH + NH_3(g) \xrightarrow[165\text{–}170\,^\circ C,\ 11\,h]{(n\text{-}Bu)Sn(OH)_2Cl,} Me(CH_2)_7CH{=}CH(CH_2)_{11}CONH_2$$
95%



$$R^1COOH + R^2NH_2 + \text{(Sn)} \xrightarrow[reflux]{p\text{-}Me_2C_6H_4} R^1CONHR^2 \qquad (1246)$$

R^1	R^2	Time (h)	Yield (%)
$Ph(CH_2)_3$	$Ph(CH_2)_2$	3	86
$Ph(CH_2)_3$	PhCH(Me)	6	81
$Ph(CH_2)_3$	$PhCH_2CH(Me)$	9	52
$Ph(CH_2)_3$	Ph	3	80
$Ph(CH_2)_3$	$(n\text{-}Bu)_2$	9	62[a]
PhCH(Et)	$Ph(CH_2)_2$	3	82
Me_3C	$Ph(CH_2)_2$	9	74
Ph	$Ph(CH_2)_2$	3	72

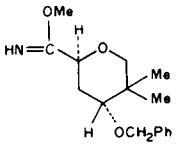
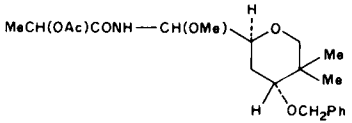
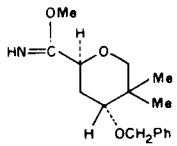
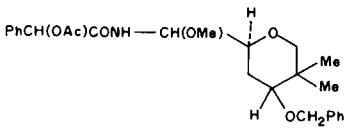
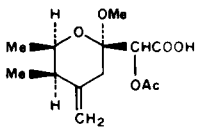
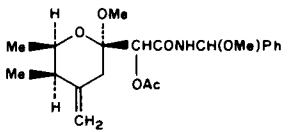
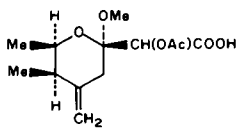
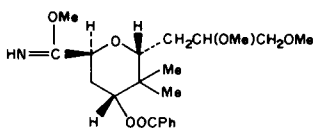
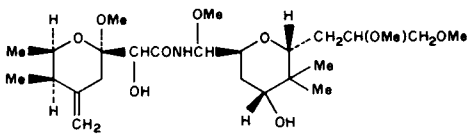
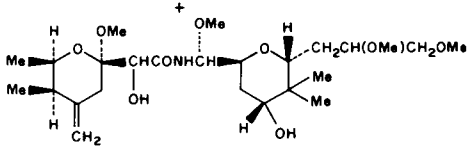
[a]Reagent used was $(n\text{-}Bu)_2NH$ and the product was disubstituted amide $Ph(CH_2)_3CON(Bu\text{-}n)_2$.

$$R^1COCl + HNR^2R^3 \longrightarrow R^1CONR^2R^3 \qquad (1247)$$

the preparation then reaction of acid chlorides with methyl imidates to produce methyl *N*-acylimidates followed by sodium borohydride reduction to produce the amide products all in one pot (equation 1248).

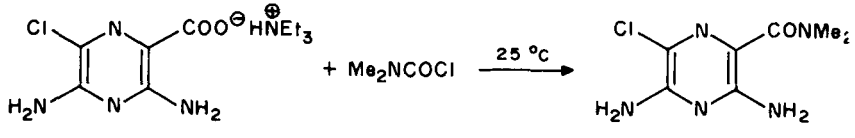
$$R^1COOH + SOCl_2 \xrightarrow[CH_2Cl_2,\ r.t.]{C_5H_5N,} R^1COCl + HN{=}C(OMe)R^2\cdot NEt_3 \longrightarrow$$

$$R^1CON{=}C(OMe)R^2 \xrightarrow[10\text{–}15\,min,\ EtOH\ or\ MeOH]{NaBH_4,\,0\,^\circ C,} R^1CONHCH(OMe)R^2 \qquad (1248)$$

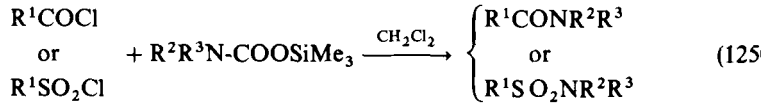
Acid	Imidate	Overall Rx time	Product	Yield (%)
MeCOOH	HN=C(OMe)Ph	7 min	MeCONHCH(OMe)Ph	85
i-PrCOOH	HN=C(OMe)Ph	11 min	*i*-PrCONHCH(OMe)Ph	85
MeCH(OAc)COOH	HN=C(OMe)Ph	11 min	MeCH(OAc)CONHCH(OMe)Ph	87[a]
PhCH(OAc)COOH	HN=C(OMe)Ph	7.5 min	PhCH(OAc)CONHCH(OMe)Ph	88[a]
MeCH(OAc)COOH		11 min		78[b]
PhCH(OAc)COOH		7.5 min		79[b]
	HN=C(OMe)Ph	10 h, 5 min		82[a]
		4.5 h		—
				—

[a] A 1:1 diastereoisomeric mixture of products.
[b] A 1:1:1 diastereoisomeric mixture of products.

Acylations can also be accomplished by the loss of a substituent other than hydrogen from the amino nitrogen. Thus, reaction of the triethylammonium salt of a carboxylic acid with dimethylcarbamoyl chloride produces[2302], with loss of carbon dioxide and chloride, an amide (equation 1249). Also, silyl-protected *N*-alkylcarbamates react with acid chlorides or sulfonyl chlorides to produce[2303], with loss of the trimethylsilyloxycarbonyl function, amides or sulfonamides, respectively (equation 1250).



(1249)

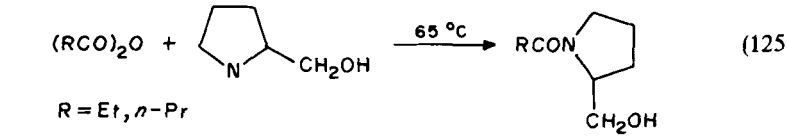


(1250)

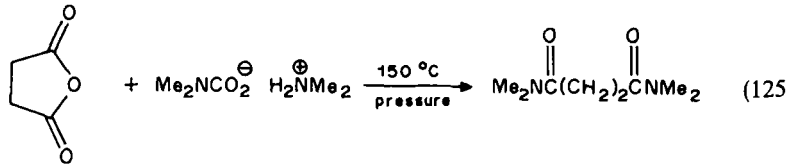
Chloride	R^2	R^3	Temp. (°C)	Time (min)	Product	Yield (%)
MeCOCl	Me	Me	r.t.	15	$MeCONMe_2$	87
MeCOCl	*n*-Pr	*n*-Pr	r.t.	15	$MeCON(Pr\text{-}n)_2$	92
$ClCH_2COCl$	Et	Et	r.t.	15	$ClCH_2CONEt_2$	89
PhCOCl	Me	Me	r.t.	15	$PhCONMe_2$	88
$PhSO_2Cl$	Me	Me	80	15	$PhSO_2NMe_2$	92
$PhSO_2Cl$	$-(CH_2)_2O(CH_2)_2-$		80	120	$PhSO_2N$-morpholino)	87

*3. Acylation with anhydrides

Recently, both symmetrical and mixed anhydrides have been used for the acylation of amines to produce amides. Reactions of symmetrical anhydrides with amines[2304] (equation 1251) and with ammonium carbamates[2305] (equation 1252) have both been reported to yield amides. However, by far, most acylations of amines have been performed using mixed anhydrides. Thus, reaction of carboxylic acids with *N*-acyl-*N*-alkyl carbamic acid produced[2306] a mixed anhydride intermediate, which when treated with ammonia gas yields the corresponding carboxamide (equation 1253).



(1251)

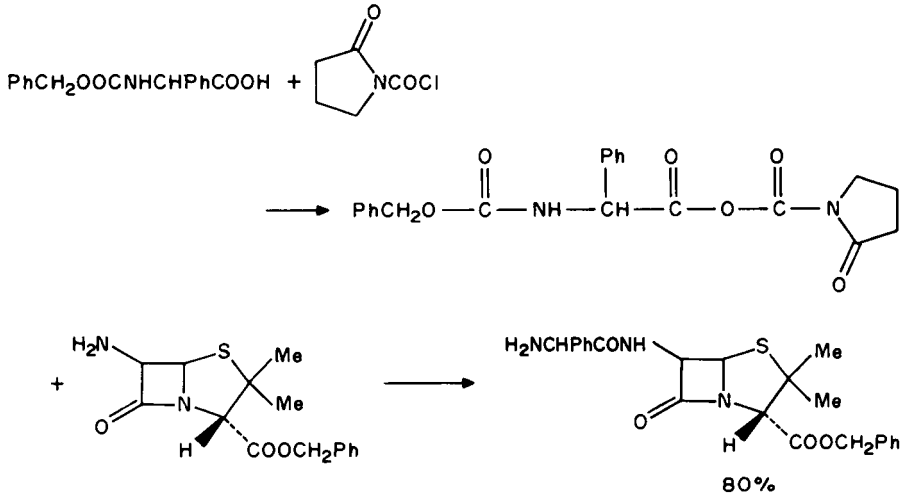


(1252)

$$PhCH_2COOH + ClOCNR^1COR^2 \rightarrow PhCH_2COOCONR^1COR^2 \xrightarrow{NH_3(g)} PhCH_2CONH_2 \quad (1253)$$

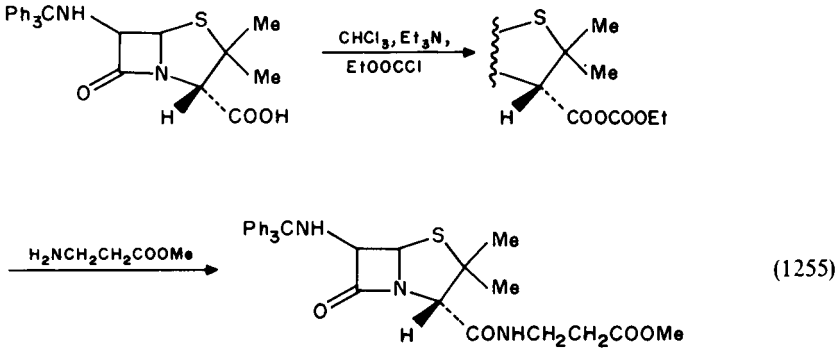
$R^1 = Ph, R^2 = Me$ or $R^1R^2 = —(CH_2)_3—$

Reaction of *N*-carbobenzoxy-protected phenylalanine with *N*-chlorocarbonyl-2-pyrrolidinone produces[2307] a mixed anhydride which, when treated with benzyl 6-aminopenicillanate, affords an 80 percent yield of the *N*-phenylalanyl-substituted penicillanate (equation 1254).



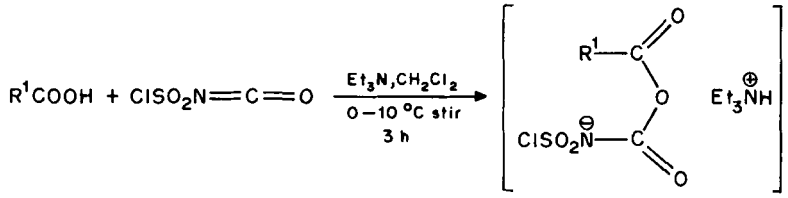
(1254)

A slightly different approach[2308] to the preparation of penam amides involves the reaction of tritylaminopenicillanic acid with ethoxycarbonyl chloride producing a mixed anhydride at the penam acid site, which upon reaction with methyl 3-aminopropionate forms the corresponding amide (equation 1255).



(1255)

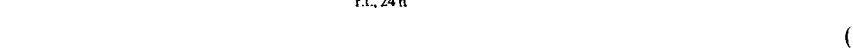
Mixed anhydrides are also the intermediates involved[2309] in the preparation of amides from carboxylic acids and chlorosulfonyl isocyanate (equation 1256).



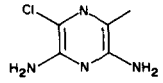
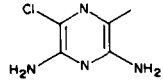
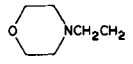
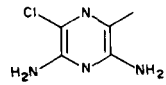
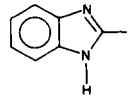
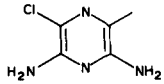
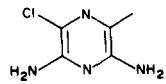
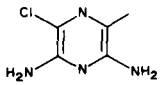
(1256)

R^1	R^2		R^3	Yield (%)
n-$C_{11}H_{23}$	Ph		H	81
$PhCH_2$	Ph		H	73
MeCH=CH	Ph		H	68
PhCH=CH	Ph		H	75
Ph	c-Hex		H	82
Ph	$PhCH_2$		H	78
Ph	Ph		H	90
Ph		$-(CH_2)_4-$		76
Ph		$-(CH_2)_5-$		76

Reaction[2310] of the triethylammonium salt of carboxylic acids with an equivalent of diphenylcarbamoyl chloride produces a carboxylic *N,N*-diphenylcarbamic anhydride which, upon reaction with amines, forms the corresponding amides (equation 1257). In

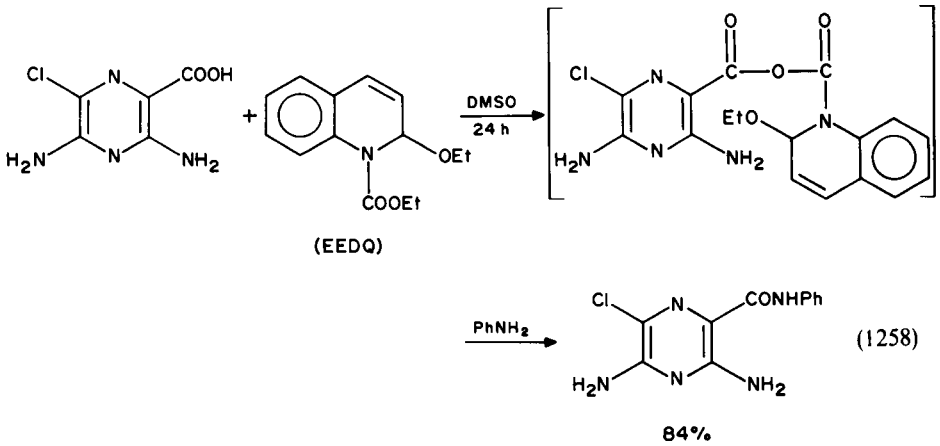


(1257)

R^1	R^2	R^3	R^1	R^2	R^3
2-Fu	$PhCH_2$	H		Ph	H
Ph	$PhCH_2$	H			H[b]
p-HOC_6H_4	$PhCH_2$	H			
p-$H_2NC_6H_4$	$PhCH_2$	H			H[a]
o-$H_2NC_6H_4$	$PhCH_2$	H			
		H[a]			H[a]
	$(EtO)_2CH$	Me[a]			

[a]THF used as solvent.
[b]DMF, 90 °C, < 2 h or THF, 25 °C, 1 h

the same reference[2310] ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate (EEDQ) was also used to form a mixed anhydride with 3,5-diamino-6-chloropyrazinecarboxylic acid, which then reacted with aniline to produce *N*-phenyl-3,5-diamino-6-chloropyrazinecarboxamide (equation 1258).



(1258)

Most of the mixed anhydride methods used to prepare amides in the recent literature involve mixed anhydrides containing phosphorus. These were prepared from a variety of phosphorus compounds such as *N,N*-dimethylphosphoramidic dichloride (DMPADC). Treatment[2311] of aromatic or aliphatic carboxylic acids with this reagent produces a mixed anhydride, which under the conditions of the reaction rearranges to produce the corresponding *N,N*-dimethyl tertiary amides (equation 1259).

In a comparison of four different methods used for the preparation of amides, published[2312] in 1980, the authors reported that the mixed anhydride method using diphenylphosphinic chloride produced the best yields. The methods compared were the dicyclohexylcarbodiimide (DCCD) method (equation 1260), the acyl carbonate method using methyl carbonochloridate (equation 1261) and using isobutyl carbonochloridate (equation 1262) and the diphenylphosphinic anhydride method (equation 1263). The results of the comparison are reported in Table 114.

$$R^1R^2C{=}CR^3COOH + DCCD \rightarrow R^1R^2C{=}CR^3COOC(=NHex\text{-}c)(NHex\text{-}c)$$

$$\xrightarrow{R^4R^5NH} R^1R^2C{=}CR^3CONR^4R^5 + R^1R^2C{=}CR^3CON(c\text{-Hex})CONHHex\text{-}c \qquad (1260)$$

(**326**) (**327**)

$$R^1R^2C{=}CR^3COOH + ClCOOMe \xrightarrow[\text{base}]{3^\circ\text{ amine}} R^1R^2C{=}CR^3COOCOOMe \xrightarrow{R^4R^5NH}$$

$$R^1R^2C{=}CR^3CONR^4R^5 + R^4R^5NCOOMe \qquad (1261)$$

(**326**) (**328**)

$$RCOOH + Me_2NPOCl_2 \xrightarrow[A \text{ or } B]{\text{Method}} [RCOOPOClNMe_2] \longrightarrow RCONMe_2 \qquad (1259)$$

Acid	Time (h)	Method[a]	Product	Yield (%)
n-$C_{10}H_{21}COOH$	96	A	n-$C_{10}H_{21}CONMe_2$	47
c-HexCOOH	96	A	c-HexCONMe$_2$	83
c-HexCOOH	—	A	c-HexCONEt$_2$[b]	58
Me$(CH_2)_7$CH=CH$(CH_2)_7$COOH (*cis*)	84	A	Me$(CH_2)_7$CH=CH$(CH_2)_7$CONMe$_2$ (*cis*)	74
Me$(CH_2)_4$(CH=CH)$_2(CH_2)_7$COOH (*cis, cis*)	84	A	Me$(CH_2)_4$(CH=CH)$_2(CH_2)_7$CONMe$_2$ (*cis, cis*)	60
PhCOOH	72	B	PhCONMe$_2$	90
o-TolCOOH	72	B	o-TolCONMe$_2$	98
o-TolCOOH	—	B	o-TolCONEt$_2$[b]	100
o-AnCOOH	72	B	o-AnCONMe$_2$	45
m-BrC_6H_4COOH	72	B	m-$BrC_6H_4CONMe_2$	94
p-$O_2NC_6H_4COOH$	60	B	p-$O_2NC_6H_4CONMe_2$	100
p-$O_2NC_6H_4COOH$	—	B	p-$O_2NC_6H_4CONEt_2$[b]	89
3,5-$(O_2N)_2C_6H_3COOH$	60	B	3,5-$(O_2N)_2C_6H_3CONMe_2$	90

[a]Method A for aliphatic acids: 5 eq. DMPADC + 1.2 eq. $Me_2N(CH_2)_2NMe_2$ in refluxing DME; Method B for aromatic acids: 10 eq. DMPADC in refluxing DME.

[b]Reagent used was *N,N*-diethylphosphoramidic dichloride (Et_2NPOCl_2) instead of the dimethyl analogue.

TABLE 114. Comparison of methods used to prepare amides[2312]

Amine			Amine		% Yield using the following method						
					Dicyclohexyl carbodiimide		Methyl carbono-chloridate		Isobutyl carbono-chloridate		Diphenylphos-phinic chloride
R^1	R^2	R^3	R^4	R^5	**326**	**327**	**326**	**328**	**326**	**329**	**326**
Me	Me	H	$PhCH_2CH_2$	H	15	42	52[a]	34[a]	57[a]	31[a]	94[a]
							60[b]	31[b]	67[b]	29[b]	85[b]
H	Me	Me	$PhCH_2CH_2$	H	19	72	40[a]	36[a]	44[a]	40[a]	83[a]
							44[b]	31[b]	49[b]	42[b]	71[b]
H	H	Me	$PhCH_2CH_2$	H	27	40	52[a]	19[a]	60[a]	16[a]	81[a]
							36[b]	14[b]	64[b]	14[b]	74[b]
c-Hex	Me	H	$PhCH_2CH_2$	H	21	65	73[a]	21[a]	76[a]	31[a]	92[a]
							76[b]	26[b]	79[b]	23[b]	79[b]
Me	Me	H	*i*-Pr	*i*-Pr	—	88	—	—	—	—	—
Me	Me	H	$—(CH_2)_5—$		35	35	24[a]	15[a]	21[a]	20[a]	61[a]
Me	Me	H	$—(CH_2)_2\text{-}O\text{-}(CH_2)_2—$		11	71	8.5[a]	12[a]	3.2[a]	24[a]	35[a]

[a]Using triethylamine as a tertiary base.
[b]Using *N*-methylmorpholine as a tertiary base.

$$R^1R^2C{=}CR^3COOH + ClCOOBu\text{-}i \xrightarrow[\text{base}]{3^\circ\ \text{amine}} R^1R^2C{=}CR^3Cr^3COOCOOBu\text{-}i \xrightarrow{R^4R^5NH} R^1R^2C{=}CR^3CONR^4R^5 + R^4R^5NCOOBu\text{-}i$$

(326) (329) (1262)

$$R^1R^2C{=}CR^3COOH + Ph_2COCl \xrightarrow[\text{base}]{3^\circ\ \text{amine}} R^1R^2C{=}CR^3COOPOPh_2 \xrightarrow{R^4R^5NH} R^1R^2C{=}CR^3CONR^4R^5 + Ph_2POOH$$

(326) (1263)

Treatment of carboxylic acids with diethylphosphorocyanidate [$(EtO)_2P(=O)CN$, DEPC] in the presence of triethylamine also produces a mixed anhydride, which is reported[2313] to be in equilibrium with a pentacovalent phosphorus compound (equation 1264). Reaction of either intermediate with an amine produces the corresponding amide (equation 1264), and this approach may also be used to produce racemization-free peptides (equation 1265).

$$\text{Bz-L-LeuOH} + \text{H-Gly-OEt·HCl} \xrightarrow[Et_3N,\ DMF,\ \text{temp., time}]{\text{DEPC}} \text{Bz-Leu-Gly-OEt} \quad (1265)$$

benzoyl-L-leucine; hydrochloride salt of glycine ethyl ester

(1265)

Temp. (°C)	Time (h)	Yield (%)	% L-Isomer
0, 20	0.5, 0.5	83	95
0, 20	0.5, 1	87	94
0, 20	0.5, 4	86	96
0, 20[a]	0.5, 4	53	95

[a] Using dimethyl phosphorocyanidate $(MeO)_2POCN$ instead of the diethyl analogue.

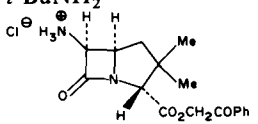
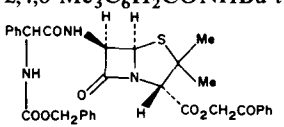
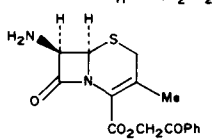
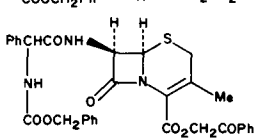
Intermediate mixed anhydrides are also involved in the one-step preparation[2314] of carboxamides using the triethylammonium salts of the carboxylic acid and monosubstituted amines in the presence of *N*-phenylphosphoramidochloridates. Three different phosphoramidochloridates were used to effect the transformation: phenyl *N*-phenylphosphoramidochloridate (**330**), *N,N*-diphenyl phosphorodiamic chloride (**331**) and phenyl *N*-methyl-*N*-phenylphosphoramidochloridate (**332**). The general reaction for this preparation is shown in equation 1266 while the results obtained are reported in Table 115.

PhOPONHPh (**330**) PhNH—PONHPh (**331**) PhO—PONMePh (**332**)

$$\textbf{326, 327, 328} + R^1COO^{\ominus}\overset{+}{H}NEt_3 \rightarrow [\text{mixed anhydride}] \xrightarrow{R^2NH_2} R^1CONHR^2 \quad (1266)$$

$$R^1COOH + DEPC \xrightarrow[0.5\ h]{Et_3N,\,0\,^\circ C,} [R^1COOPO(OEt)_2] \rightleftharpoons R^1COOP(OEt)_2 \xrightarrow[r.t.,\,1\,h]{R^2R^3NH} R^1CONR^2R^3 \qquad (1264)$$

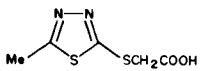
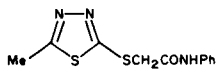
NC O⊖

Acid	Amine	Time (h)	Product	Yield (%)
PhCOOH	*c*-HexNH$_2$	1	PhCONHHex-*c*	97
PhCOOH	*c*-HexNH$_2$	24[a]	PhCONHHex-*c*	70
PhCOOH	*c*-HexNH$_2$	24[b]	—	0
PhCOOH	*n*-BuNH$_2$	1	PhCONHBu-*n*	94
PhCOOH	Et$_2$NH	1	PhCONEt$_2$	91
m-TolCOOH	Et$_2$NH	1	*m*-TolCONEt$_2$	86
PhCH$_2$COOH	PhNH$_2$	1	PhCH$_2$CONHPh	83
Me(CH$_2$)$_4$COOH	PhNH$_2$	1	Me(CH$_2$)$_4$CONHPh	84
Me(CH$_2$)$_4$COOH	PhCH$_2$NH$_2$	1	Me(CH$_2$)$_4$CONHCH$_2$Ph	85
2,4,6-Me$_3$C$_6$H$_2$COOH	*n*-BuNH$_2$	20	2,4,6-Me$_3$C$_6$H$_2$CONHBu-*n*	43
2,4,6-Me$_3$C$_6$H$_2$COOH	*t*-BuNH$_2$	70	2,4,6-Me$_3$C$_6$H$_2$CONHBu-*t*	9
2,4,6-Me$_3$C$_6$H$_2$COOP(OEt)$_2$	*t*-BuNH$_2$	24[c]	2,4,6-Me$_3$C$_6$H$_2$CONHBu-*t*	35
PhCH(NHCOOCH$_2$Ph)COOH		24[d]		71
PhCH(NHCOOCH$_2$Ph)COOH		6[d]		100

[a] No Et_3N.
[b] Using DCCD in DMF.
[c] Mixed anhydride and DMF used.
[d] DMF used as solvent.

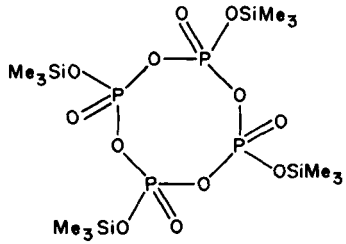
TABLE 115. Preparation of amides using *N*-phenylphosphoramidochloridates[2314]

Acid	Chloridate	Amine	Reaction			
			Method[a]	Time (min)	Product	Yield (%)
PhCOOH	**330**	$PhNH_2$	A	30	PhCONHPh	95
PhCOOH	**331**	$PhNH_2$	A	30	PhCONHPh	42
PhCOOH	**332**	$PhNH_2$	A	210	PhCONHPh	61
PhCOOH	**330**	*c*-$HexNH_2$	B	90	PhCONHHex-*c*	70
PhCOOH	**330**	*c*-$HexNH_2$	C	45	PhCONHHex-*c*	90
p-ClC_6H_4COOH	**330**	$PhNH_2$	A	20	*p*-$ClC_6H_4CONHPh$	93
o-ClC_6H_4COOH	**330**	*p*-$TolNH_2$	A	60	*o*-$ClC_6H_4CONHTol$-*p*	94
o-ClC_6H_4COOH	**330**	*c*-$HexNH_2$	C	30	*o*-$ClC_6H_4CONHHex$-*c*	90
2-$ThiCH_2COOH$	**330**	$PhNH_2$	A	60	2-$ThiCH_2CONHPh$	97
2-PyrCOOH	**330**	*p*-$TolNH_2$	A	60	2-PyrCONHTol-*p*	94
$PhCH_2COOH$	**330**	$PhNH_2$	A	60	$PhCH_2CONHPh$	94
$PhCH_2COOH$	**330**	*o*-$TolNH_2$	A	60	$PhCH_2CONHTol$-*o*	93
$PhCH_2COOH$	**332**	*o*-$TolNH_2$	A	210	$PhCH_2CONHTol$-*o*	50
PhCH=CHCOOH *trans*	**330**	$PhNH_2$	A	45	PhCH=CHCONHPh *trans*	90
t-BuCOOH	**330**	$PhNH_2$	A	90	*t*-BuCONHPh	91

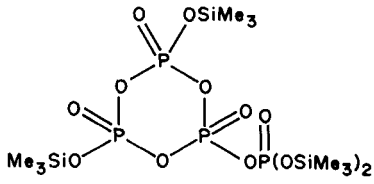
PhCHClCOOH	**330**	$PhNH_2$	A	30	PhCHClCONHPh	98
PhCHClCOOH	**330**	p-$ClC_6H_4NH_2$	A	30	PhCHClCONHC$_6$H$_4$Cl-p	97
PhCHClCOOH	**330**	c-$HexNH_2$	B	30	PhCHClCONHHex-c	70
PhCHClCOOH	**330**	c-$HexNH_2$	C	45	PhCHClCONHHex-c	90
PhCHClCOOH	**330**	p-$MeCOC_6H_4NH_2$	A	60	PhCHClCONHC$_6$H$_4$COMe-p	90
PhCHClCOOH	**330**	PhCH(COOC$_3$H$_7$-i)NH$_2$	B	60	PhCHClCONHCH(COOC$_3$H$_7$-i)Ph	80
PhCHClCOOH	**330**	PhCH(COOC$_3$H$_7$-i)NH$_2$	C	60	PhCHClCONHCH(COOC$_3$H$_7$-i)Ph	91
N-PhthalimidoCH$_2$COOH	**330**	$PhNH_2$	A	30	N-PhthalimidoCH$_2$CONHPh	96
N-PhthalimidoCH$_2$COOH	**331**	$PhNH_2$	A	60	N-PhthalimidoCH$_2$CONHPh	60
N-PhthalimidoCH$_2$COOH	**332**	$PhNH_2$	A	150	N-PhthalimidoCH$_2$CONHPh	43
N-PhthalimidoCH$_2$COOH	**330**	$PhCH_2NH_2$	B	60	N-PhthalimidoCH$_2$CONHCH$_2$Ph	71
N-PhthalimidoCH$_2$COOH	**330**	$PhCH_2NH_2$	B	45	N-PhthalimidoCH$_2$CONHCH$_2$Ph	90
N-PhthalimidoCH$_2$COOH	**330**	$EtO_2CCH_2NH_2$	B	60	N-PhthalimidoCH$_2$CONHCH$_2$COOEt	80
N-PhthalimidoCH$_2$COOH	**330**	$EtO_2CCH_2NH_2$	C	60	N-PhthalimidoCH$_2$CONHCH$_2$COOEt	95
	**330**	$PhNH_2$	A	30		90

[a]Method: A, reagent + acid + Et_3N + amine in CH_2Cl_2 and the mixture stirred at room temperature for 30–90 minutes.
B, reagent + acid + Et_3N in CH_2Cl_2, stir for 5 minutes at room temperature; then amine + Et_3N in CH_2Cl_2 added dropwise during 20 minutes at room temperature and the mixture stirred for 60 minutes.
C, reagent + acid + Et_3N in CH_2Cl_2, stir for 15 minutes at room temperature; Et_3N, then amine added and the mixture stirred at room temperature for 60 minutes.

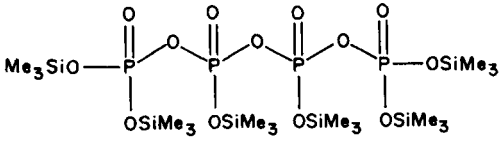
Amides and amidines have been prepared[2315,2316] by the reaction of carboxylic acids and amines in the presence of polyphosphoric acid trimethylsilyl ester (PPSE), which is a mixture of cyclotetraphosphate (**333**), isocyclotetraphosphate (**334**), linear tetraphosphate (**335**) and a small amount of pyrophosphate (**336**). Unlike polyphosphoric acid (PPA), PPSE is soluble in aprotic solvents such as benzene, chlorinated hydrocarbons and sulfolane. Reactions of carboxylic acids with one equivalent of amine produced amides (equation 1267), but this approach was found to be best suited for the synthesis of symmetrical amidines (equation 1268) and unsymmetrical amidines (equation 1269).



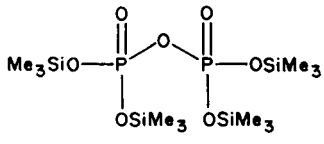
(**333**)



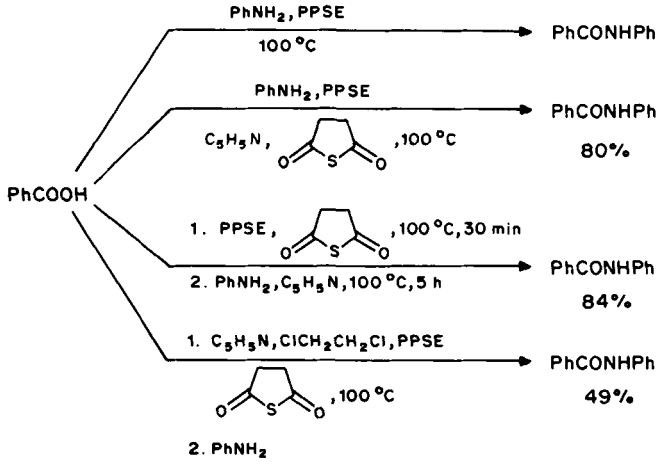
(**334**)



(**335**)



(**336**)

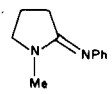


(1267)

$$R^1COOH + 2R^2NH_2 \xrightarrow[5\text{ h, no solvent}]{\text{PPSE, 160 °C}} R^1{-}\overset{\overset{NR^2}{\|}}{C}{-}NHR^2 \qquad (1268)$$

R^1	Amine	Product	Yield (%)
Ph	$PhNH_2$	PhC(NHPh)=NPh	83
p-An	$PhNH_2$	*p*-AnC(NHPh)=NPh	87
p-ClC_6H_4	$PhNH_2$	*p*-ClC_6H_4C(NHPh)=NPh	88
p-$O_2NC_6H_4$	$PhNH_2$	*p*-$O_2NC_6H_4C$(NHPh)=NPh	84
c-Hex	$PhNH_2$	*c*-HexC(NHPh)=NPh	81
n-Pen	$PhNH_2$	*n*-PenC(NHPh)=NPh	79
PhCH=CH	$PhNH_2$	PhCH=CHC(NHPh)=NPh	65
Ph	*p*-$AnNH_2$	PhC(NHAn-*p*)=NAn-*p*	88
Ph	*p*-$TolNH_2$	PhC(NHTol-*p*)=NTol-*p*	87
Ph	*p*-$ClC_6H_4NH_2$	PhC(NHC_6H_4Cl-*p*)=NC_6H_4Cl-*p*	69
Ph	*p*-$O_2NC_6H_4NH_2$	PhC(NH$C_6H_4NO_2$-*p*)=N$C_6H_4NO_2$-*p*	82

$$R^1\overset{\overset{O}{\|}}{C}NR^3R^4 + R^2NH_2 \xrightarrow[5\text{ h, no solvent}]{\text{PPSE, 160 °C}} RC(=NR^2)NR^3R^4 \qquad (1269)$$

Amide	Amine	Product	Yield (%)
PhCONHPh	*p*-$AnNH_2$	PhC(NHPh)=NAn-*p*	97
PhCONHPh	*p*-$O_2NC_6H_4NH_2$	PhC(NHPh)=N$C_6H_4NO_2$-*p*	91
PhCONHPh	*n*-$PenNH_2$	PhC(NHPh)=NPen-*n* +	23
		PhC(NHPh)=NPh	53
PhCONHPh	*c*-$HexNH_2$	PhC(NHPh)=NHex-*c*	54
PhCONHPh	*t*-$BuNH_2$	PhC(NHPh)=NBu-*t*	87
PhCONHMe	$PhNH_2$	PhC(NHMe)=NPh	94
$MeCONMe_2$	$PhNH_2$	$MeC(NMe_2)$=NPh	89
	$PhNH_2$		85

(Trimethylsilyl)ethoxyacetylene, which is a stable and easy-to-handle reagent, serves as an excellent dehydrating agent for the synthesis[2317] of amides from the corresponding carboxylic acids (equation 1270).

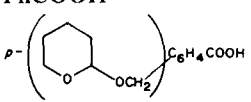
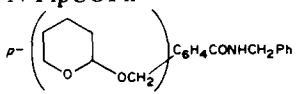
Two sulfonyl chloride reagents have been used to produce amides from carboxylic acids via mixed anhydride intermediates. Thus, reaction of carboxylic acids with methanesulfonyl chloride in pyridine produces[2318] a mixed sulfonic anhydride which upon further reaction with ammonia gas produces the unsubstituted amide (equation 1271). The amides formed were not isolated however, but were further reacted with methanesulfonyl chloride to produce the corresponding nitriles (equation 1272).

$$RCOOH + MeSO_2Cl \xrightarrow{C_5H_5N} RCOOSO_2Me \xrightarrow[0\text{ °C}]{NH_3(g)} RCONH_2 \quad \text{(not isolated)} \qquad (1271)$$

acids used: 3-nitrobenzoic, 4-methoxybenzoic, 4-chlorobenzoic, cinnamic, stearic, 2-carbomethoxynicotinic and 4-carbomethoxynicotinic.

$$RCONH_2 + MeSO_2Cl \longrightarrow RC{\equiv}N \qquad (1272)$$

$$R^1COOH + Me_3SiC{\equiv}COEt \xrightarrow[2.\ r.t.,\ stir\ 2\,h]{1.\ HgO,\ 0\,^\circ C} R^1C(=O)-O-C(=CHSiMe_3)-OEt \xrightarrow[CH_2Cl_2,\ r.t.]{R^2R^3NH} R^1CONR^2R^3 \qquad (1270)$$

Acid	Amine	Conditions[a]	Product	Yield (%)
MeCOOC(OEt)=CHSiMe$_3$[b]	$PhNH_2$	20 °C, 4 h	MeCONHPh	94
MeCOOC(OEt)=CHSiMe$_3$[b]	$PhCH_2NH_2$	20 °C, 1.5 h	$MeCONHCH_2Ph$	100
MeCOOC(OEt)=CHSiMe$_3$[b]	$Ph(CH_2)_2NH_2$	20 °C, 3 h	$MeCONH(CH_2)_2Ph$	97
MeCOOC(OEt)=CHSiMe$_3$[b]	PhNHMe	40 °C, 9 h	MeCONMePh	94
MeCOOH	$PhCH_2NH_2$	Method A: 20 °C, 3.5 h	$MeCONHCH_2Ph$	92
MeCOOH	$Ph(CH_2)_2NH_2$	Method B: 20 °C, 8 h	$MeCONHCH_2Ph$	94
EtCOOH	$PhCH_2NH_2$	Method B: 40 °C, 2 h	$EtCONHCH_2Ph$	86
EtCOOH	PhNHMe	Method A: 20 °C, 1.5 h	EtCONMePh	86
EtCOOH	$PhCH_2NHMe$	Method B: 60 °C, 3.5 h	$EtCONMeCH_2Ph$	80
t-BuCOOH	$PhCH_2NH_2$	Method B: 80 °C, 3 h	*t*-$BuCONHCH_2Ph$	81
PhCOOH	$PhCH_2NH_2$	Method A: 20 °C, 21 h	$PhCONHCH_2Ph$	85
PhCOOH	$Ph(CH_2)_2NH_2$	Method A: 20 °C, 6 h 40 °C, 8 h	$PhCONH(CH_2)_2Ph$	91
PhCOOH	$Ph(CH_2)_2NH_2$	Method B: 40 °C, 13 h	$PhCONH(CH_2)_2Ph$	88
PhCOOH	Piperidine	Method A: 20 °C, 9 h	N-PipCOPh	100
	$PhCH_2NH_2$	Method B: 40 °C, 8 h		83

[a]Method A: 2-step process; Method B: 1-step process.
[b]Intermediate prepared by reaction of MeCOOH with $Me_3SiC{\equiv}COEt$.

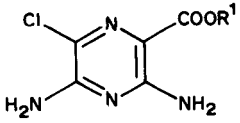
The other sulfonyl chloride reagent used was sulfuryl chloride fluoride which, upon reaction with carboxylic acids, produced[2319] the acylfluorosulfonate mixed anhydride. Reaction of these mixed anhydrides with primary amines afforded the corresponding monosubstituted amide (equation 1273).

$$R^1COOH + SO_2ClF \xrightarrow[CH_2Cl_2,\ r.t.,\ stir\ 1\ h]{Et_3N,\ N_2,} RCOOSO_2F \xrightarrow[Et_3N,\ r.t.,\ stir\ 1\ h]{R^2NH_2,\ CH_2Cl_2,} R^1CONHR^2 \quad (1273)$$

R^1	R^2	Yield (%)	R^1	R^2	Yield (%)
H	Me	65	p-$O_2NC_6H_4$	Ph	80
Me	Ph	70	$PhCH_2$	Ph	85
Ph	Ph	70	$PhCH_2$	$PhCH_2$	96
Ph	t-Bu	80	c-C_7H_{13}	c-Hex	81
Ph	c-Hex	90	o-$HO_2CC_6H_4$	Ph	85

*4. *Acylation with esters*

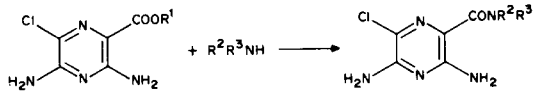
The conversion of carboxylic acid esters to amides by reaction with amines has always been a difficult conversion to accomplish due to the limited acylating ability of the esters. This fact has again been confirmed by reports, such as the one[2320] dealing with the synthesis of amides from pyrazinecarboxylic acid esters. Although some amides have been successfully prepared[2320] from esters of pyrazinecarboxylic esters as shown in equation 1274, many amide preparations with this class of substrate have been unsuccessful (equation 1275).



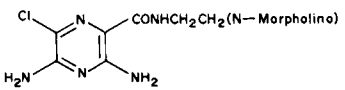
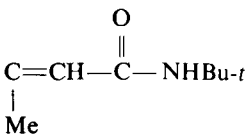
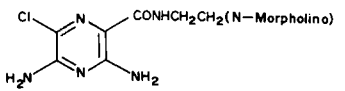
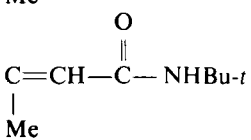
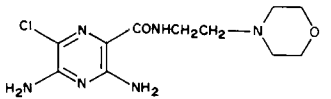
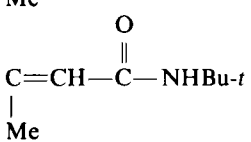
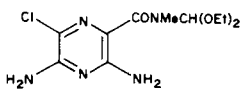
$$+ R^2R^3NH \longrightarrow N.R. \quad (1275)$$

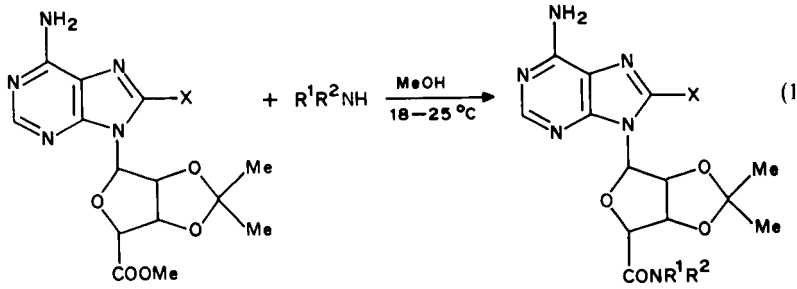
R^1	Amine	Conditions
Me	N-Morpholino$CH_2CH_2NH_2$	DMF, 90 °C, 2 h
CMe=CHCONHBu-t	$HNMeCH(OEt)_2$	THF, 25 °C, stir, 4 h
CMe=CHCONHBu-t	$PhNH_2$	THF, 25 °C, stir, 24–48 h
CMe=CHCONHBu-t	2-Amino-1,2,3-triazole	THF, reflux, 24 h
CMe=CHCONHBu-t	2-Amino-1,3-thiazole	THF, reflux,
CMe=CHCONHBu-t	2-Aminobenzimidazole	THF, reflux,

Primary, as well as mono- and disubstituted amides of 8-substituted-2′,3′-*O*-isopropylideneadenosine-5′-carboxylate (equation 1276) and 8-substituted adenosine-5′-carboxylate (equation 1277) have been prepared[2321] by reactions of the corresponding methyl and ethyl esters, respectively, with the appropriate amine substrate at room temperature.



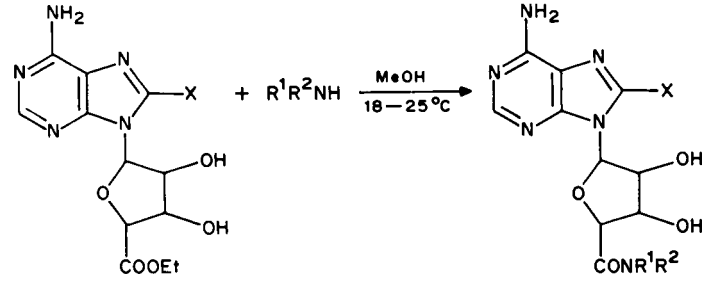
(1274)

R^1	Amine	Conditions	Product	Yield (%)
CH_2CN	N-Morpholino $CH_2CH_2NH_2$	DMF, 90 °C, 2 h		20
	N-Morpholino$CH_2CH_2NH_2$	DMF, 90 °C, < 2 h		—
	N-Morpholino$CH_2CH_2NH_2$	THF, 25 °C, 1 h		100
	$HNMeCH(OEt)_2$	THF, reflux, 18 h		73



(1276)

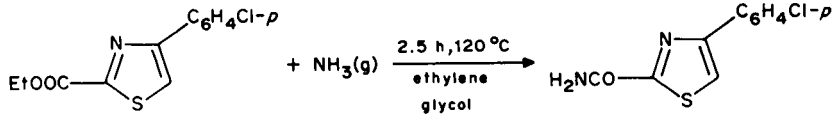
X = Br, NH_2, MeNH, Me_2N, EtNH, SH
$R^1R^2NH = H_2N$, MeNH, Me_2N, EtNH
(when X = Br and $R^1R^2NH = H_2N$, 82% yield is obtained)



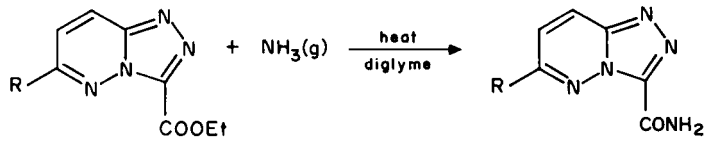
(1277)

(X and R^1R^2NH are the same as reported in equation 1276)

Unsubstituted amide formation from esters which traditionally react poorly or not at all with ammonia in aqueous or alcoholic solutions at room temperature has been achieved[2322] when the ammonia was bubbled for 2–5 hours through an ethylene glycol or diglyme solution of the ester at 100 to 150 °C (equation 1278). This approach was also successful[2322] with esters of pyridazine derivatives (equation 1279).



(1278)



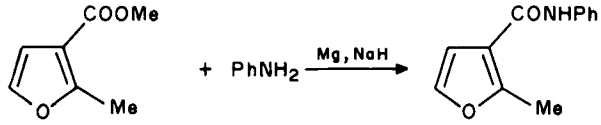
(1279)

R = Cl, $HOCH_2CH_2O$, $HOCH_2CH_2NH$

Another approach to the preparation of amides from carboxylic acid esters involves[2323] the reaction of the esters with an excess of aniline in the presence of magnesium or aluminum anilide (equation 1280).

$$R^1COOR^2 + PhNH_2 \xrightarrow[\text{anilide}]{\text{Mg or Al}} R^1CONHPh \qquad (1280)$$

Specific example



In the presence of sodium methoxide, carboxylic acid esters react with urea or *N,N,N',N'*-tetrasubstituted ureas to produce[2324] the corresponding amides or *N,N*-disubstituted amides (equation 1281).

$$RCOOH \begin{cases} \xrightarrow[\text{NaOMe, 100–150 °C}]{H_2NCONH_2} RCONH_2 \\ \xrightarrow[\text{NaOMe, 100–150 °C}]{R^1R^2NCONR^1R^2} RCONR^1R^2 \end{cases} \qquad (1281)$$

$R = C_{1-10}$ alkyl, aralkyl, alkoxyalkyl, Ph, ClC_6H_4, etc.
R^1 and $R^2 = C_{1-4}$ alkyl or NR^1R^2 = piperidino, morpholino

By reaction[2325] of the trimethylsilyl esters of carboxylic acids with *N*-(trimethylsilyl)diethylamine at 130–160 °C in DMF or in the presence of a catalytic amount of DMF, the corresponding diethylamide is produced (equation 1282).

$$RCOOSiMe_3 + Me_3SiNEt_2 \xrightarrow[130\ 160\,°C]{DMF} RCONEt_2 \qquad (1282)$$

$R = Et_2N$, Ph, $CH_2{=}CH$, $CH_2{=}CHCH_2NH$

Reaction of amines and carbonyl-activated borolane esters has proved[2326] to be an effective method for the production of amides (equation 1283) of nonanoic acid.

$$\xrightarrow{RNH_2} n\text{-}C_8H_{17}CONHR + HOB \qquad (1283)$$

Amine	Product[a]	Yield (%)
$PhCH_2NH_2$	n-$C_8H_{17}CONHCH_2Ph$	92
Pyrolidine	n-$C_8H_{17}CO$(N-Pyrrolidinyl)	85

(*continued*)

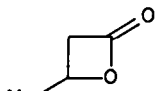
Amine	Product[a]	Yield (%)
n-$BuNH_2$	n-$C_8H_{17}CONHBu$-n	84
Morpholine	n-$C_8H_{17}CO$(N-Morpholino)	74
$PhCH_2NHMe$	n-$C_8H_{17}CONMeCH_2Ph$	74
$EtOOCCH_2NH_2$	n-$C_8H_{17}CONHCH_2COOEt$	63

[a]Obtained by inverse addition of the nonanoxyborane to the amine (2 equivalents) in THF at − 78 °C.

Direct conversion of esters into primary amides by uncatalyzed aminolysis using primary amines is difficult, while the corresponding reaction using secondary amines had never been reported. However, in the recent literature, the preparation of both primary and secondary amides from carboxylic esters and amines has been reported[2327] to occur at room temperature to 30–45 °C if the reaction is performed under 8 kilobars of pressure. In addition, no inert atmospheres or dry solvents were required to accomplish this conversion (equation 1284). A similar reaction occurs[2327] when β-butyrolactone is treated with diphenylamine at 45 °C under 8 kilobars of pressure, but in this case both an amide and an acid are formed depending upon the site of attack of the amine (equation 1285).

$$R^1COOR^2 + HNR^3R^4 \xrightarrow{8\ kbar} R^1CONR^3R^4 \qquad (1284)$$

R^1	R^2	R^3	R^4	Temp. (°C)	Yield (%)
n-$C_8H_{17}CH{=}CH(CH_2)_7$	Me	$-(CH_2)_4-$		35	100
n-$C_8H_{17}CH{=}CH(CH_2)_7$	Me	$-(CH_2)_5-$		35	100
$PhCH_2$	Me	$-(CH_2)_4-$		35	100
$PhCH_2$	Me	$-(CH_2)_5-$		35	100
$PhCH_2$	Me	Et	Et	45	67
$PhCH_2$	Me	$PhCH_2$	H	35	100
Ph	Et	$-(CH_2)_4-$		r.t.	100
Ph	Et	$-(CH_2)_5-$		35	81
PhCH(OH)	Me	$-(CH_2)_4-$		35	96
PhCH(OH)	Me	$-(CH_2)_5-$		100	77
PhCH(OH)	Me	$PhCH_2$	H	35	90
c-Hex	Me	$-(CH_2)_4-$		45	89
c-Hex	Me	$-(CH_2)_5-$		45	98
$NCCH_2CH_2$	Me	$-(CH_2)_4-$		35	100
$NCCH_2CH_2$	Me	$-(CH_2)_5-$		35	100



$$+\ Ph_2NH \xrightarrow[8\ kbar]{45\ °C} MeCH(OH)CH_2CONPh_2\ (28\%) + MeCH(NPh_2)CH_2COOH\ (35\%) \qquad (1285)$$

*5. *Acylation with ketenes and isocyanates*

Both isocyanides and isocyanates have been reacted with carboxylic acids to produce intermediates, which are then treated with amines to produce amides. Thus, reaction of carboxylic acids or protected dipeptides with t-butylisocyanide produces[2328] the intermediate [(acyloxy)methylene]t-butylamine which, upon reaction with amines, affords the

$$R^1COOH + CNBu\text{-}t \longrightarrow [R^1COOCH{=}NBu\text{-}t] \xrightarrow[\substack{4\ days\\ 20\,^\circ C}]{R^2NH_2} R^1CONHR^2 \qquad (1286)$$

Acid	Amine	Product[a]	Yield[b] (%)
$PhCOOH$	$PhCH_2NH_2$	$PhCONHCH_2Ph$	30
$PhCHEtCH_2COOH$	$MeCH(NH_2)COOEt$	$Me{-}CH(NHCOCH_2CHPhEt){-}COOEt$	18–23
$MeCHCOOH$ | $NHCOOCH_2Ph$	$MeCH(NH_2)COOEt$	$MeCHCONHCHCOOEt$ | $NHCOOCH_2Ph$	45–46
$Me_2CHCHCOOH$ | $NHCOOCH_2Ph$	H_2NCH_2COOMe	$Me_2CHCHCONHCH_2COOMe$ | $NHCOOCH_2Ph$	24
N-PhthalimidoCH$_2$COOH	$MeCH(NH_2)COOEt$	N-PhthalimidoCH$_2$CONHCHMeCOOEt	55
$Me_2CHCHCOOH$ | $NHCOPh$	H_2NCH_2COOMe	$Me_2CHCHCONHCH_2COOMe$ | $NHCOPh$	52–81
$Me_2CHCHCOOH$ | $NHCOPh$	$MeCH(NH_2)COOEt$	$MeCHCHCONHCHMeCOOEt$ | $NHCOPh$	48–90

[a] All amino acids are in their L form.
[b] Variation in yields depends upon solvent used and whether $ZnCl_2$ was added.

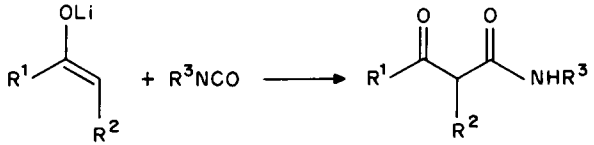
corresponding amides (equation 1286). When isocyanates are used as a reactant the intermediate formed loses carbon dioxide to produce[2329] an amide derived from the carboxylic acid and the isocyanate only without any added amine (equation 1287).

$$R^1COOH + R^2N{=}C{=}O \xrightarrow[\substack{Ar,\ 60\,^\circ C,\\ MeC_6H_5,\ 2\,h}]{Et_3N,} [R^1COOCONHR^2] \xrightarrow{-CO_2} R^1CONHR^2 \qquad (1287)$$

Acid	Isocyanate	Product	Yield (%)
$ClCH_2COOH$	$ClCH_2CH_2NCO$	$ClCH_2CONHCH_2CH_2Cl$	82
$PhCH_2CH_2COOH$	$ClCH_2CH_2NCO$	$PhCH_2CH_2CONHCH_2CH_2Cl$	73
$PhCH_2COOH$	$ClCH_2CH_2NCO$	$PhCH_2CONHCH_2CH_2Cl$	47
$PhCH_2COOH$	PhNCO	$PhCH_2CONHPh$	31[a]
PhCOOH	$ClCH_2CH_2NCO$	$PhCONHCH_2CH_2Cl$	53
PhCOOH	PhNCO	PhNHCONHPh	48
PhCOOH	p-$O_2NC_6H_4NCO$	$PhCONHC_6H_4NO_2$-p	59
PhCOOH	$ClCH_2NCO$	$PhCONH_2$	—
$Me_2C{=}CHCOOH$	$ClSO_2NCO$	$Me_2C{=}CHCONHSO_2Cl$[a]	—

[a]The product isolated after hydrolysis is $Me_2C{=}CHCONH_2$.

A convenient new method for the preparation of β-keto amides involves reaction of ketone lithium enolates with aryl and alkylisocyanates (equation 1288)[2330].



(1288)

$R^1, R^2 = Ph, H$
$R^1\ R^2 = Ph, Me$
$R^1, R^2 = t\text{-}Bu, H$

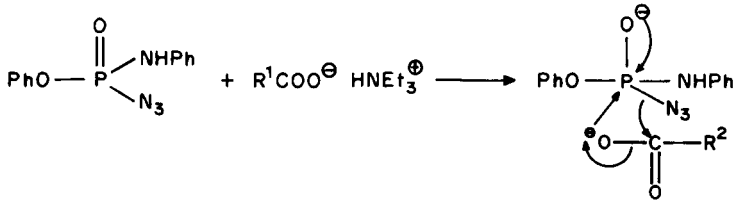
Isocyanate intermediates have also been involved in the preparation[2331] of *N,N'*-disubstituted ureas via a modified Curtius reaction using phenyl *N*-phenylphos-

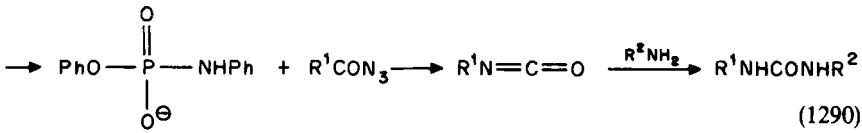
$$PhOP(O)(N_3)NHPh + Ar^1COOH + Ar^2NH_2 \xrightarrow[\substack{solvent,\\ reflux}]{Et_3N,} Ar^1NHCONHAr^2 \qquad (1289)$$

Acid	Amine	Solvent	Time (h)	Yield (%)
PhCOOH	$PhNH_2$	MeCN	1.5	94
PhCOOH	$H_2NC_5H_4N$[a]	MeCN	1.5	80
PhCOOH	$H_2NC_5H_4N$[a]	C_6H_6	2	40
o-ClC_6H_4COOH	o-$ClC_6H_4NH_2$	MeCN	1.5	87
p-ClC_6H_4COOH	$PhNH_2$	MeCN	1.5	90
p-ClC_6H_4COOH	$PhNH_2$	C_6H_6	2	38

[a]The reference does not specify the location of the amine function in relation to the nitrogen of the pyridine ring.

phoramidoazidate. This approach[2331] is a one-step procedure which requires that the carboxylic acid, amide and phosphoramidoazidate be refluxed in a solvent in the presence of triethylamine (equation 1289). The mechanism of this reaction clearly shows its Curtius nature as well as the formation of the isocyanate intermediate (equation 1290).

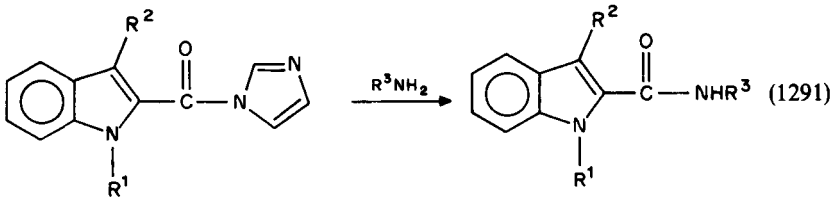




(1290)

*6. *Transamidation*

Two types of transamidation reactions of carboxamides have been reported recently. The first and most general type of transamidation involves the reaction of the carboxamides with an amine which results in the transfer of the acyl group of the amide to the nitrogen of the amine. Examples of this reaction include the preparation[2332] of indole-2-carboxamides from imidazolides using amines (equation 1291), the preparation[2333] of

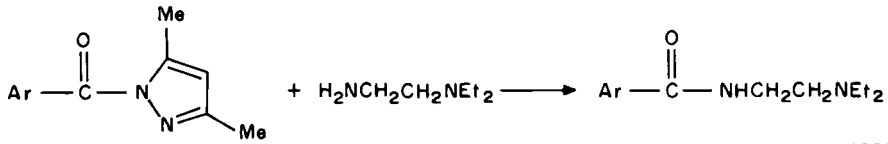


(1291)

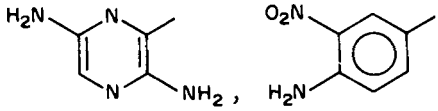
R^1 = H, Me

R^2 = H, CHO

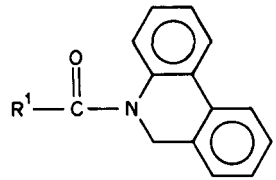
R^3 = CH_2CH_2COOEt, $CHMeCOOEt$, CH_2COOEt, $CH(COOEt)_2$, Me, Et, *n*-Bu, *i*-Bu, *c*-Hex, $PhCH_2$



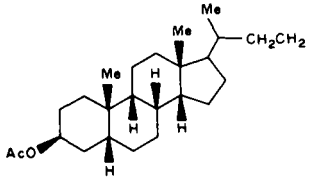
(1292)

Ar = 

amino carboxylic and pyrazine amides from amino carboxylic acid pyrazine pyrazolides using 2-(diethylamino)ethylamine (equation 1292) and the preparation[2334] of simple amides from 5-acyl-5,6-dihydrophenanthridines by reaction with primary amines in the presence of ceric pyridinium chloride and cupric oxide (equation 1293).



(1293)

R^1	R^2	Yield (%)
$Ph(CH_2)_3$	$Ph(CH_2)_2$	82
$Ph(CH_2)_3$	MeCH | Ph	85
Ph	(L) $Me_2CHCH_2CHCOOEt$	94
n-Pr	$Ph(CH_2)_2$	79
EtCH | Ph	MeCH | Ph	70
$Br(CH_2)_{10}$	$Ph(CH_2)_2$	85
$Br(CH_2)_{10}$	$Ph(CH_2)_2$	76
	$Ph(CH_2)_2$	84[a]

[a]This reaction was carried out in a mixture of 1,2-dichloroethane and acetonitrile.

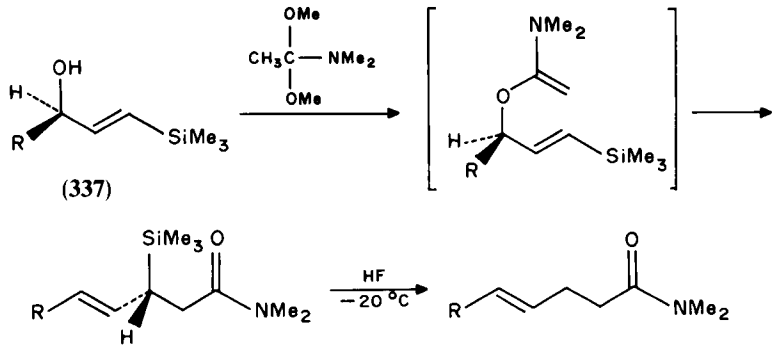
The second, less common type of transamidation involves the exchange of the acyl function of a carboxylic acid for the acyl function of an amide. One example of this type of transamidation reaction[2335] involves the reaction of acetamide with 1-adamantanecarboxylic acid to produce the corresponding 1-adamantanecarboxamide (equation 1294). The product yields are increased if the reaction is performed in the presence of manganese acetate as a catalyst.

$$\text{1-Ad-Z-COOH} + CH_3CONH_2 \longrightarrow \text{1-Ad-Z-CONH}_2 \qquad (1294)$$

Z = bond, CH_2; 1-Ad = 1-adamantyl

*C. Amides by Rearrangements

3-(Trimethylsilyl)allyl alcohols (**337**) undergo amide acetal Claisen rearrangement to form (*E*)-β,γ-unsaturated amides and esters via the reaction sequence shown in equation 1295[2336].



(1295)

*D. Amides by Oxidation

Although it has been reported[2337-2339] that the cyano group is stable in the presence of superoxides in benzene[2337], pyridine[2338], acetonitrile[2339] or 18-crown-6 ether solvents, reaction of nitriles with sodium superoxide in dimethyl sulfoxide at room temperature effects[2340] conversion to the corresponding amide (equation 1296). It was also observed[2340] that the addition of nitrobenzene produces an unambiguous increase in the rate of conversion of these nitriles to the corresponding amides.

$$RCN + NaO_2 \xrightarrow[\text{r.t.}]{Me_2SO} RCONH_2 \qquad (1296)$$

Nitrile	Time (h)	Amide	Yield (%)
n-$C_{11}H_{23}CN$	8	n-$C_{11}H_{23}CONH_2$	70
c-HexCN	7	c-HexCONH$_2$	85
PhCN	6	PhCONH$_2$	78
1,3-$C_6H_4(CN)_2$	2	1,3-$C_6H_4(CONH_2)_2$	85
o-ClC_6H_4CN	16	o-$ClC_6H_4CONH_2$	80
o-$MeOC_6H_4CN$	3	o-$MeOC_6H_4CONH_2$	80
p-$MeOC_6H_4CN$	21	p-$MeOC_6H_4CONH_2$	88
p-$Me_2C(NO_2)C_6H_4CN$	5	p-$Me_2C(NO_2)C_6H_4CONH_2$	68
2,6-$Cl_2C_6H_3CN$	31	2,6-$Cl_2C_6H_3CONH_2$	81
2,4,6-$Me_3C_6H_2CN$	7	2,4,6-$Me_3C_6H_2CONH_2$	73
p-EtOOCC$_6$H$_4$CN	5[a]	p-HOOCC$_6$H$_4$CONH$_2$	96

[a] Minutes.

Treatment of carboxylic acid hydrazides with cupric chloride in the presence of amines produces[2341] good yields of the corresponding amides (equation 1297). The mechanism proposed[2341] for this conversion involves the initial formation of an acyl cation, which upon nucleophilic attack by the amine anion produces the corresponding amide (equation 1298).

$$R^1CONHNH_2 + CuCl_2 \xrightarrow[\text{r.t. } R^2R^3NH]{\text{THF, } N_2} R^1CONR^2R^3 \qquad (1297)$$

R	R^2R^3NH	Yield (%)
n-C_7H_{15}	NH_3[a]	93
n-C_7H_{15}	Pyrrolidine	16–99[b]
n-C_7H_{15}	Pyrrolidine[c]	96
n-C_7H_{15}	Morpholine	96
n-C_7H_{15}	Morpholine[c]	93
n-C_7H_{15}	i-$BuNH_2$[c]	92
Ph	NH_3[a]	89
Ph	Pyrrolidine	94
Ph	Pyrrolidine[c]	95
Ph	Morpholine	94
Ph	Morpholine[c]	95
Ph	i-$BuNH_2$[c]	93

[a] A THF solution saturated with ammonia was used.
[b] Yields vary depending upon the number of moles of amine used.
[c] Using a $CuCl_2$–diazabicycloundecene (DBU) complex.

$$\begin{aligned} RCONHNH_2 + 3CuClNR^2R^3 &\longrightarrow R\dot{C}O + 3CuCl + 3HNR^2R^3 + N_2 \\ R\dot{C}O + CuClNR^2R^3 &\longrightarrow R\overset{\oplus}{C}O + CuCl + R^2R^3N^{\ominus} \\ R\overset{\oplus}{C}O + R^2R^3N^{\ominus} &\longrightarrow RCONR^2R^3 \end{aligned} \qquad (1298)$$

*F. Amides by Carboxamidation

Reaction of carbon monoxide with the complex reducing agent CoCRA, a mixture of sodium hydroxide, sodium t-amyloxide and cobalt acetate, produces a cobalt carbonyl species, CoCRACO, which has been found[2342] to be effective in the carbonylation of bromobenzene at atmospheric pressure. If the reaction is performed in the presence of an amine, then three products are obtained: the corresponding benzamide, t-amyl benzoate and benzoic acid (equation 1299).

$$PhBr + \text{amine} \xrightarrow[\substack{\text{CO, THF, 63 °C} \\ \text{2. } H_3O^{\oplus}}]{\text{1. NaH, } t\text{-}C_5H_{11}ONa, Co(OAc)_2} PhCON\!- + + PhCOOC_5H_{11}\text{-}t + PhCOOH \qquad (1299)$$

Amine	Time (h)	% Yield of Amide	ester	acid
n-$BuNH_2$	48[a]	30–35	0–5	10–15
n-$C_8H_{17}NH_2$	40[a]	40–45	5–10	10–15
c-$HexNH_2$	20[a]	70–75	Trace	5–10
c-$HexNH_2$	35[b]	55–60	0–5	5–10
Et_2NH	45[a]	40–45	20–25	5–10
Et_2NH	60[b]	40–45	0–5	0–5
i-Pr_2NH	25[a]	30–35	30–35	15–20
$C_5H_{11}NH$	25[a]	45–50	5–10	15–20
$C_5H_{11}NH$	25[b]	50–55	5–10	10–15

[a] NaH/t-AmONa/amine/$Co(OAc)_2$/PhBr = 40/20/40/10/20 mM.
[b] NaH/t-AmONa/amine/$Co(OAc)_2$/PhBr = 100/20/100/10/50 mM.

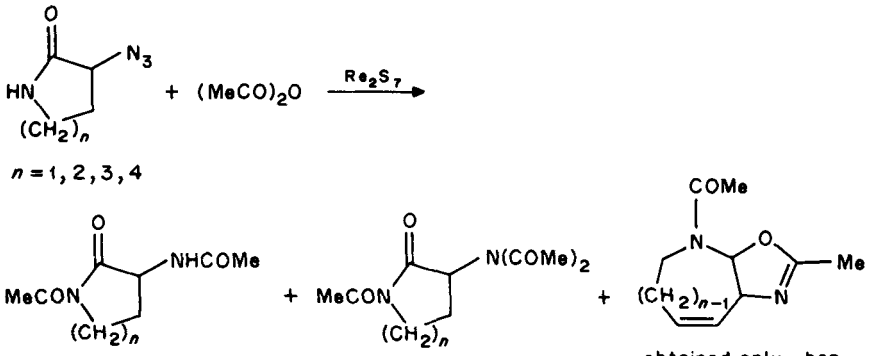
***H. Amides by Miscellaneous Methods**

Conversion of the azo groups of α-azidocarboxylic acid amides to an *N*-acetylated group has been reportedly[2343] accomplished in one step by the addition of acetic anhydride in the presence of rhenium oxide catalysts (equation 1300). The products from these reactions are the corresponding *N*-mono- and *N*,*N*-diacylated dehydroamino acid amides. Similarly, treatment of α-azido lactams with dirhenium heptasulfide affords[2343] the corresponding cyclic analogues (equation 1301).

$$R^1R^2CHCHCONR^3R^4 + (MeCO)_2O \xrightarrow[90\,^\circ C]{NaReO_4} \underset{N_3}{\underset{|}{}}$$

$$R^1R^2CH{=}C(NHCOMe){-}CONR^3R^4 + R^1R^2CH{=}C(N(COMe)_2){-}CONR^3R^4 \qquad (1300)$$

$R^1 = n\text{-}C_3H_7$, $R^2 = H$, $R^3 = H$, $R^4 = CH_2Ph$ and R^1, R^2, R^3, $R^4 = Me$



(1301)

Treatment of phenols, thiophenols, alcohols or thiols with a primary or secondary amine, a saturated or unsaturated monoketone and chloro-, bromo- or iodoform in the presence of benzyltriethylammonium chloride and a base produces[2344] the corresponding 2-alkoxy- or alkylthiocarboxamide (equation 1302).

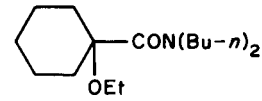
$$R^1R^2CHZH + R^3R^4NH + R^5COR^6 + CHX_3 \xrightarrow[\text{base}]{PhCH_2NEt_3Cl^-} R^5R^6CCONR^3R^4$$
$$\underset{ZCHR^1R^2}{\underset{|}{}}$$

$Z = O$ or S $\quad X = Cl, Br, I$ (1302)

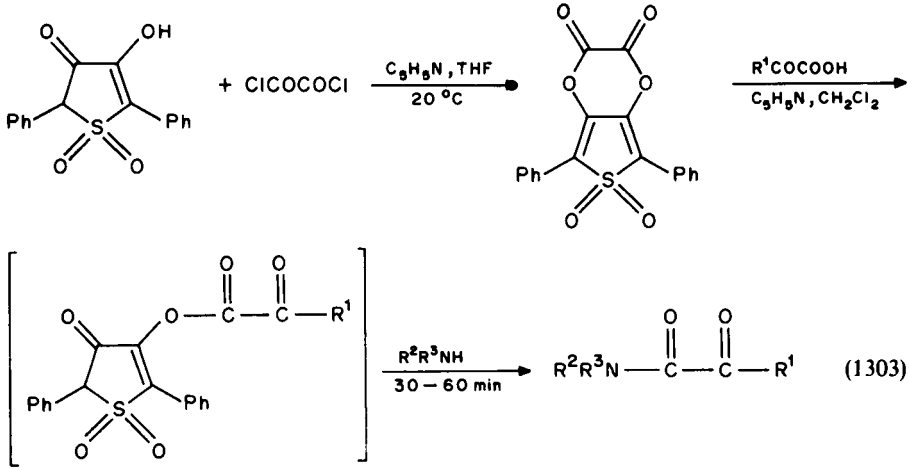
R^1, R^2, R^3, R^4, R^5, R^6 = alkyl or aryl

Alcohol or thiol	Amine	Ketone	CHX_3	Product
PhSH	Et_2NH	Me_2CO	$CHCl_3$	$Me_2C(SPh)CONEt_2$
EtSH	$n\text{-}Pr_2NH$	Me_2CO	$CHCl_3$	$Me_2C(SEt)CON(n\text{-}Pr)_2$

(continued)

Alcohol or thiol	Amine	Ketone	CHX_3	Product
EtOH	n-Bu_2NH	Cyclohexanone	$CHCl_3$	
PhOH	MePhNH	EtCOMe	$CHCl_3$	EtMeC(OPh)CONMePh

Reaction of the diphenyl substituted cyclic sulfone, 4-hydroxy-3-oxo-2,5-diphenyl-2,3-dihydrothiophen-1,1-dioxide, with oxalyl chloride in pyridine and tetrahydrofuran produces[2345] 2,3-dioxo-5,7-diphenyl-2,3-dihydrothieno[3,4-*b*][1,4]dioxin-6,6-dioxide in 93–99 percent yield. Further reaction of this product with an α-ketocarboxylic acid produces an intermediate ester, which is not isolated but which is allowed to react with an amine to produce the corresponding 2-oxocarboxamides (equation 1303).



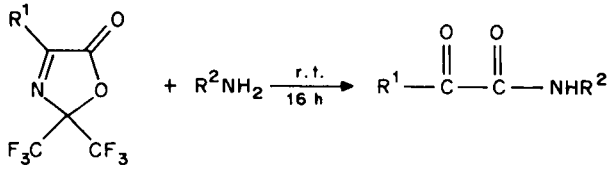
(1303)

R^1	R^2	R^3	Yield (%)
Me	H	$PhCH_2$	85
Me	Et	Et	84
Me	—$(CH_2)_5$—		78
Ph	H	$PhCH_2$	76
Ph	Et	Et	78
Me	H	(L)-MeCHCOOMe	81
Me	H	(L)-(*i*-Pr)CHCOOMe	85
Me	H	(*i*-Pr)CH_2CHCOOH	75
Me	Me	$MeOOCCH_2$	68
Me	(L)—$CH(CH_2)_3$— COOMe		65
Et	H	CH_2COOEt	55
$PhCH_2$	Me	CH_2COOMe	18
Me	H_2N	Ph	60
Me	H_2N	2,4-$(NO_2)_2C_6H_3$	95

Although a portion of this preparation may be viewed as the production of amides from an ester, the overall reaction involves the preparation of amides from a cyclic sulfone which relegates this preparative method to this section.

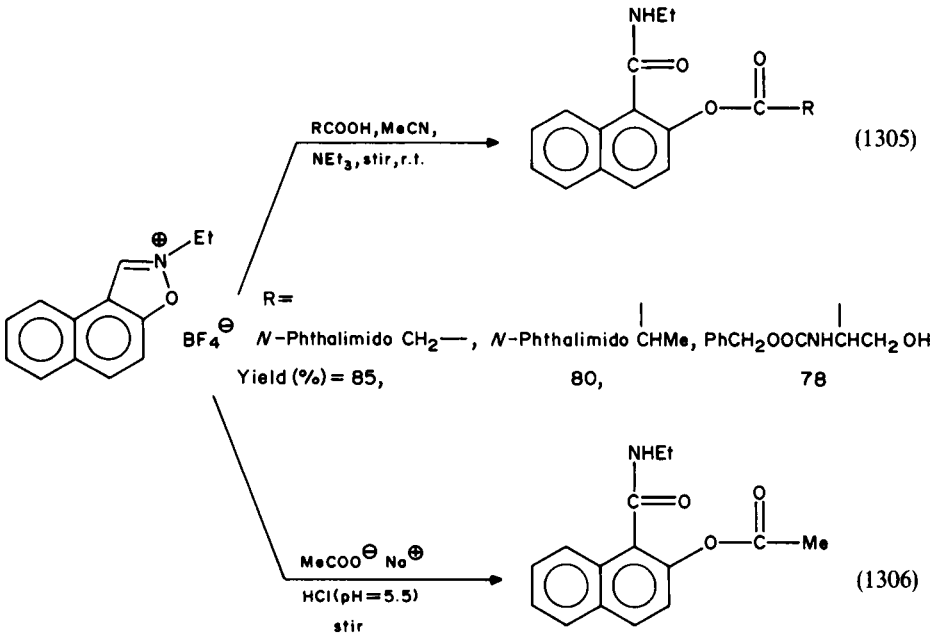
2-Oxocarboxamides have also been prepared[2346] by the reaction of 4-alkyl-2,2-bis(trifluoromethyl)-2*H*-oxazol-5-ones with amines (equation 1304).

A similar kind of ring opening which leads to production of ester amides is reported[2347] to occur when *N*-ethylnaphth(1,2-*d*)isoxazolium fluoroborate is treated with a carboxylic



(1304)

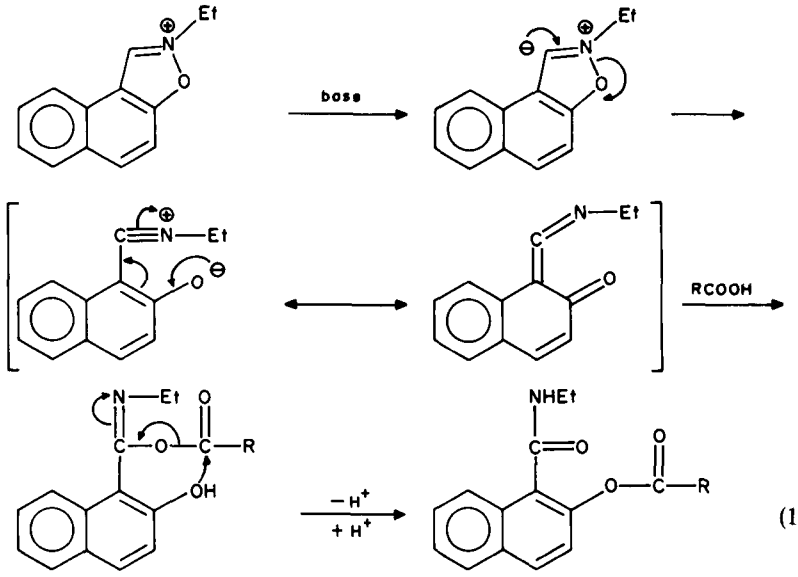
R^1	R^2	Conditions	Yield (%)
Me	Ph	MeCOOH	85
Me	CH_2COOMe	Et_3N, THF	50
Me	CH(Me)COOMe	Et_3N, THF	58
Me	$Me_2CHCHCOOMe$	Et_3N, THF	72
Me	$PhCH_2CHCOOMe$	Et_3N, THF	70
Et	Ph	MeCOOH	80
Ph	Ph	MeCOOH	76
$PhCH_2$	Ph	MeCOOH	88



(1305)

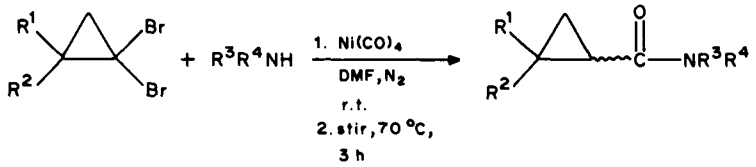
(1306)

acid (equation 1305) or a carboxylic acid salt (equation 1306). The reported[2347] mechanism for this reaction involves initial reaction of the *N*-ethylnaphth(1,2-*d*)isoxazolium fluoroborate with the base to form a ylide intermediate, which rearranges to an intermediate naphthoketo-keteneimine which then reacts with the carboxylic acid (equation 1307).



(1307)

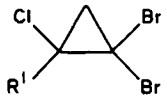
Treatment of *gem*-dibromocyclopropanes with amines in the presence of nickel tetracarbonyl affords[2348] the corresponding cyclopropanecarboxamides (equation 1308). Extension of this reaction[2349,2350] to 1,1-dibromo-2-chlorocyclopropanes produced mainly ring-opened carboxamides as the major products (equation 1309), probably via condensation of an intermediate nickel enolate[2349–2351].



(1308)

R^1	R^2	Amine	Yield (%)	*trans:cis* ratio
Ph	H	*n*-$PrNH_2$	0–78[a]	45:55
Ph	H	$PhNH_2$	63	50:50
Ph	H	Pyrrolidine	66	—
Ph	H	CH_2=$CHCH_2NH_2$	56	—
Me	COOMe	Pyrrolidine	44	—

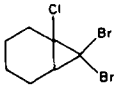
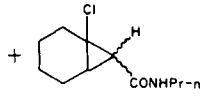
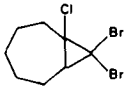
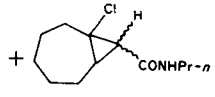
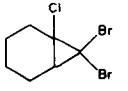
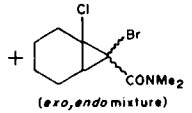
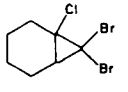
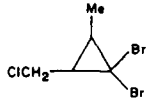
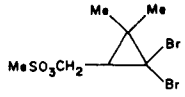
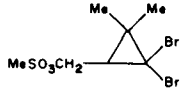
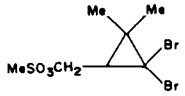
[a]The variation in yield is caused by the varying ratios of molar equivalents of amine to nickel tetracarbonyl employed.



$$+\ R^2NH_2 \xrightarrow[\text{DMF, 70 °C}]{\text{Ni(CO)}_4} CH_2{=}CR^1CH_2CONHR^2 + CH_2{=}CR^1CH(CONHR^2)_2$$

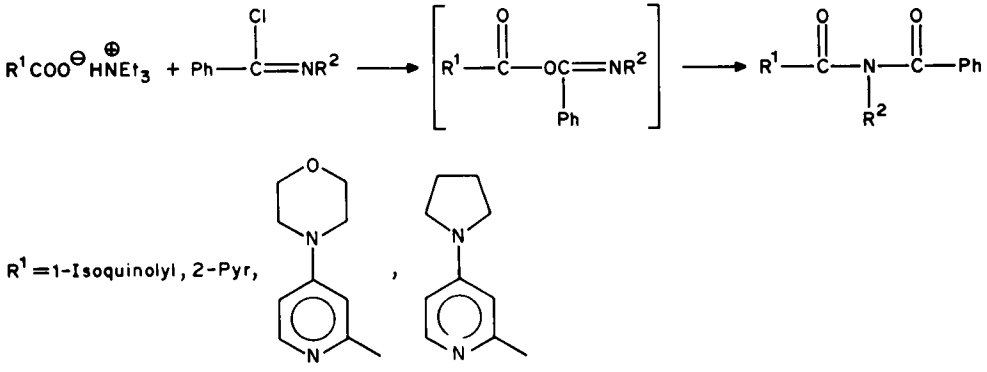
3 h

(1309)

Substrate	Amine	Product	% Yield (ratio)
	n-$PrNH_2$	1-Cyclohexenyl $CH_2CONHPr$-n + 1-Cyclohexenyl $CH(CONHPr\text{-}n)_2$ +  (*exo,endo* mixture)	62 (37:39:24)
	n-$PrNH_2$	1-Cycloheptenyl $CH_2CONHPr$-n + 1-Cycloheptenyl-$CH(CONHPr\text{-}n)_2$ +  (*exo,endo* mixture)	74 (43:38:19)
	Me_3SiNMe_2	1-Cyclohexenyl CH_2CONMe_2 + 1-Cyclohexenyl $CH(CONMe_2)_2$ +  (*exo,endo* mixture)	55 (36:51:13)
	Me_3SiNMe_2 + PhCHO	1-Cyclohexenyl-C(=CHPh)[a]-$CONMe_2$	31
	n-$PrNH_2$	$CH_2{=}CHCHMeCH_2CONHPr$-n	30
	n-$PrNH_2$	$CH_2{=}CHCMe_2CH_2CONHPr$-n	34
	Et_2NH	$CH_2{=}CHCMe_2CH_2CONEt_2$	15
	Me_3SiNMe_2	$CH_2{=}CHCMe_2CH_2CONMe_2$	46

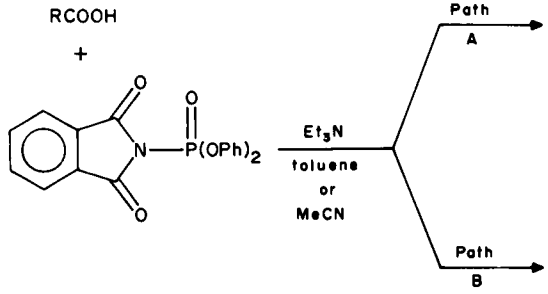
*VII. SYNTHESIS OF IMIDES

Few articles have appeared in the recent literature which report new methods of preparation for imides. Of those reported two are noteworthy. The first[2352] involves the preparation of unsymmetrical imides by reaction of the triethylamine salt of heteroaromatic carboxylic acids with phenylarylimino chloride and proceeds via an intramolecular oxygen to nitrogen acyl migration (equation 1310), while the second report[2353] describes



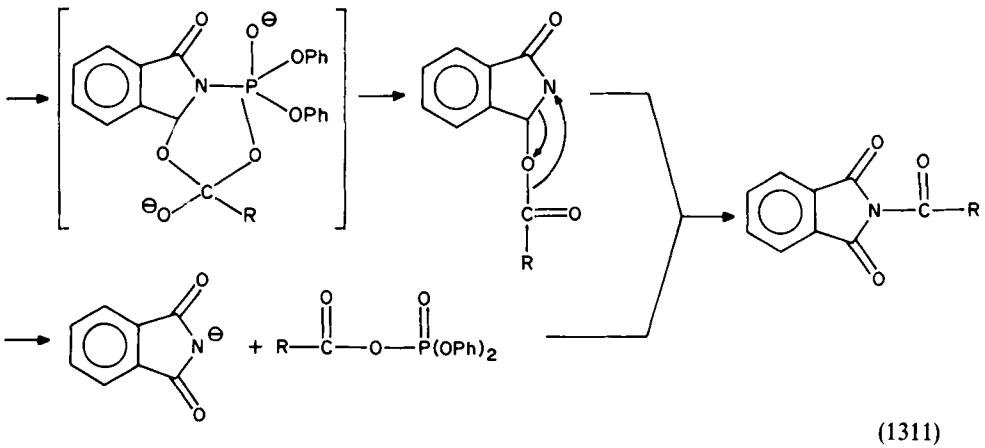
(1310)

the preparation of *N*-acylphthalimides from carboxylic acids and diphenylphosphorophthalimide. The mechanism proposed[2353] for this reaction involves a mixed phosphoric–carboxylic acid anhydride of two kinds. The first, obtained by Path A, undergoes elimination followed by a sigmatropic rearrangement to produce the product, while the second, obtained via Path B, undergoes nucleophilic attack at the carbonyl carbon by the phthalimide anion, to produce the product (equation 1311).

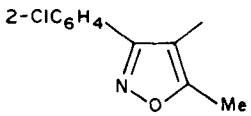


(continued)

[a]This product was also obtained using the same starting material, $Ni(CO)_4$ and Me_3SiNMe_2 in benzene[2349].



(1311)

R	Solvent	Time (h)	Yield (%)
Me	Toluene	2	85
Et	MeCN	4	89
n-Pr	Toluene	2	85
n-Bu	Toluene	2	80
t-Bu	Toluene	3	75
Ph	MeCN	3	88
p-ClC_6H_4	MeCN	3	85
PhCH=CH	Toluene	2	80
N-PhthalimidoCH$_2$	Toluene	0.5	50
N-PhthalimidoCHMe	Toluene	2	81
3-Pyr	Toluene	2	67
	Toluene	1	93

*VIII. ACKNOWLEDGMENTS

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